Progress Report
1998-2002

ATTENTION GROUP PROGRESS REPORT

Overview

The attention programme addresses the twin problems of selective perception and cognitive control. Together, these have become central issues in modern cognitive neuroscience (Desimone & Duncan, 1995; Miller & Cohen, 2000), with rapid progress deriving from well-defined behavioural questions and a basis in known sensorimotor physiology.

Together, our Projects address problems of visual, auditory and tactile attention, spatial cognition, consciousness, executive function and intelligence.

Project A1 focuses on visual selective attention. In a series of papers published in the previous funding period and interregnum (Desimone & Duncan, 1995; Duncan, Humphreys & Ward, 1997) we introduced a neurophysiological model of attentional functions. This integrated competition model was based on a series of behavioural, neuropsychological and neurophysiological studies, including four Nature papers over this period (Chelazzi, Miller, Duncan, & Desimone, 1993; Duncan, Ward, & Shapiro, 1994; Duncan, Martens, & Ward, 1997; Humphreys, Romani, Olson, Riddoch, & Duncan, 1994). Work based on this model is now a focus in many major laboratories (e.g. Kastner, De Weerd, Desimone, & Ungerleider, 1998; O'Craven, Downing, & Kanwisher, 1999; Rees, Frackowiak, & Frith, 1997). In our own work, we have addressed the contributions of prestriate, inferotemporal and prefrontal cortex to attentional function (Everling, Tinsley, Gaffan, & Duncan, 2002, Nature Neuroscience). In neuropsychological work, we have related components of our physiological model to deficits in a well-specified formal model of attentional function (Bundesen, 1990; see Duncan et al., 1999, Journal of Experimental Psychology: General). In new behavioural studies, we have addressed separation and integration of visual attention, auditory attention and response selection. Preliminary experiments using functional neuroimaging have also appeared.

Project A2 focuses on spatial representation, spatial impairment, and the development of mutually beneficial links between theoretical advance and clinical application. The work on impairment has three main themes. The first lies in the relationship between persistent pathological spatial bias and supervisory processes engaged in the maintenance of alert, goal-directed states (e.g., Robertson, Mattingley, Rorden, & Driver, 1998b). In addition to informing experimental development and effective clinical intervention with adults, this work has led to the prediction, demonstration, and remediation of spatial bias in children with executive deficits of developmental origin (e.g., Manly, Robertson, & Verity, 1997). The second theme concerns interactions between motor planning/initiation and spatial awareness in brain damaged adults and in children (e.g. Dobler et al., 2001a). A final theme in impairment concerns experimental analysis of cross-modal competition/enhancement of spatial representations (e.g., Mattingley, Driver, Beschin, & Robertson, 1997) and the effects of right parietal damage on non-visual representation (e.g. Farrell & Robertson, 2000). One strong aspiration has been to make the results of the work relevant and accessible to clinical audiences. Accordingly, publications in clinically directed journals and book chapters have accompanied more theoretical dissemination, including in Nature and Psychological Bulletin. Work on normal intact people has demonstrated the effect of perceptual contact with a structured environment on frame of reference and self-location (Marcel & Dobel, in press) and has led to discovery of individual differences in tactile fusion and allochiria that may underlie differential manifestations of spatial neglect with brain damage (Project A2.5).

Project A3 investigates the selective perception of sounds ("Auditory Scene Analysis") by healthy individuals, stroke patients, and deaf people fitted with a cochlear implant. It combines behavioural experiments with the capacity to perform EEG and functional imaging experiments at the CBU and elsewhere in Cambridge. We have shown that the build-up of auditory streaming is critically dependent on attention in healthy individuals, and that streaming is reduced in the contralesional ear of stroke patients, diagnosed with unilateral neglect on the basis of performance on visual tasks (Carlyon, Cusack, Foxton, & Robertson, 2001, Journal of Experimental Psychology: Human Perception and Performance). Taken together, these two findings provide the first evidence that cortical processes are involved in auditory streaming (as opposed to the consequences of streaming simply being measurable in cortex). Further constraints on the neural basis for auditory scene analysis were imposed by an EEG study of the continuity illusion, performed in collaboration with Pulvermüller and colleagues (Micheyl et al., in press, Journal of Cognitive Neuroscience). The study, which used the mismatch negativity technique, demonstrated the first neurophysiological correlate of an auditory illusion in human listeners. We have also applied our knowledge of auditory scene analysis to an important clinical population. Many cochlear implant users can understand speech in quiet, but even the most successful experience difficulty in segregating competing sounds. This research benefits from strong clinical collaborations with Addenbrooke's hospital, Cambridge, and with research groups worldwide. Together with colleagues in Melbourne, Australia, we have developed sophisticated hardware and software allowing us to apply arbitrary patterns of electrical stimulation to the auditory nerve. This has allowed us to identify some of the cues that implantees can and cannot use to separate two competing sounds, and to develop a model of how listeners perceive a mixture of sounds applied to one channel of their implant (Carlyon, van Wieringen, Long, Deeks, & Wouters, 2002, Journal of the Acoustical Society of America; McKay & Carlyon, 1999, Journal of the Acoustical Society of America).

Project A4 deals with consciousness, attention and bodily experience. In a variety of studies over the last two funding periods we have made several conceptual contributions to the study of consciousness and attention. One of these has been fractionation of consciousness (a) into first- and second-order consciousness corresponding to phenomenal experience and awareness, and (b) into split and disunified consciousness at each level (Marcel, 1993, 1994, 1998; Marcel, Tegnèr & Nimmo-Smith, in press). This has led to a new analysis of anosognosia for plegia following stroke (Marcel et al., in press). A forthcoming issue of the Journal of Consciousness Studies (Eds Jack & Roepstorf) will be devoted to issues raised by this. We have also extended the topic to cover bodily experience, action and emotion (Marcel, 2000, Marcel, in press-b; Lambie & Marcel, 2002). Indeed our theoretical paper on emotion experience in Psychological Review (Lambie & Marcel, 2002) integrating emotion, cognition and neuropsychology, although only recent, has had a major impact on different areas of psychology and on philosophers, leading to invited presentations at the International Society for Emotion Research (July, 2002) and at the American Psychological Association (2003). Introduction of the role of two neglected aspects of attention (self vs world focus; immersion vs detachment) has informed and led to work on touch and awareness of action (Gallagher & Marcel, 1999; Marcel, in press-b; Marcel et al., in press).

In Project A5 we turn to cognitive control, and in particular the functions of prefrontal cortex. Until recently, it was widely accepted that the lateral frontal cortex was organised according to information content, dorsolateral and ventrolateral prefrontal cortex being specialized for respectively spatial and object working memory (e.g. Goldman-Rakic, 1994). Previous and continuing work by Owen (Owen, Evans, Petrides, 1996a; Owen, Doyon, Petrides, Evans, 1996b) has largely overturned this view; as now widely accepted, complexity of processing rather than information content is the key consideration in prefrontal specialization. Our new work has dealt more fully with the functions of ventrolateral prefrontal cortex, addressing links between its role in memory processes and its role in attention. Functions of orbitofrontal cortex have been explored with further emphasis on integration with lateral frontal regions. Addressing hemispheric asymmetry, we have questioned the conventional view that left and right prefrontal cortex are strongly specialized for (respectively) memory encoding and retrieval. Building on all these results, we have recently put forward a new general view of prefrontal function (Duncan, 2001a, Nature Reviews Neuroscience; see also Duncan & Owen, 2000a). Rather than strict regional specialization, this model proposes substantial flexibility in the function of prefrontal neurons. Such flexibility may help account for our neuroimaging results, recently reported in Science, suggesting a key role for prefrontal cortex in general intelligence (Duncan et al., 2000). Finally, functional neuroimaging, psychopharmacological and neuropsychological studies in Parkinson's disease have been combined to investigate functional interactions between discrete nuclei of the basal ganglia and their corresponding targets within the frontal lobe. These studies have important theoretical and clinical implications and, with over 15 publications, represent one of the most extensive bodies of work in this area worldwide (for review see Owen, 1997).

Project A6, as with A2, is based on the synthesis of theoretically driven and clinically applied work, here in the context of non-spatially-specific attentional and executive disorders. The close links with Evans and colleagues at the Oliver Zangwill Centre for Neuropsychological Rehabilitation have been important in binding clinically relevant studies with more exploratory projects including functional neuroimaging (Manly et al., submitted-b), electrophysiology (Datta et al., submitted) and studies with healthy volunteers (e.g., Manly, Lewis, Robertson, Watson, & Datta, 2001b). To date, few systematic attempts have been made in the rehabilitation of such disorders and, as the key capacities that usually facilitate change are compromised, it is an inherently challenging task. Preliminary results using environmental cues to trigger executive reviews have been positive (e.g., Manly, Hawkins, Evans, & Robertson, 2001a). Elements of A6 have also informed the development of assessment tools for children, including the Test of Everyday Attention for Children (Manly et al., 2002a), itself the subject of a recent symposium of the International Neuropsychological Society. In clinically pioneering work with patients diagnosed as persistent vegetative state (Menon et al., 1998; Owen et al., in press), Owen has worked with the team at the Wolfson Brain Imaging Centre to demonstrate the potential of functional neuroimaging in the diagnosis and management of this difficult condition. This work has attracted considerable attention from scientists and clinicians internationally, as well as from the world's press.

This work is firmly in line with the core CBU remit of integrating cognitive and brain systems theory. Our methods include cognitive studies in normal and clinical groups, functional neuroimaging, event-related potentials, and psychopharmacology. The work is also in line with the goal of two-way interaction between basic science and clinical application, with both assessment of clinical methods based on theoretical work, and new theoretical questions deriving directly from clinical practice. Much of this clinically-oriented work (Projects A2, A6) was initially proposed by Dr I. Robertson; following his departure in 1999, these projects (along with the new proposals in Project A3) have been under the scientific direction of Dr T. Manly.

The programme is closely dependent on links to other Cambridge groups. The bulk of our functional imaging programme, both in normal subjects and clinical groups, depends on the collaborative input and facilities of the Wolfson Brain Imaging Centre (in particular, Professors J. Pickard and E. Bullmore). In maintaining and using the Cambridge Cognitive Neuroscience Research Panel, we depend on regular research meetings with Dr N. Antoun of the Addenbrooke's Department of Radiology, with additional input from the Addenbrooke's MRIS Unit. Clinical aspects of our programme, including work in rehabilitation and cochlear implants, depend on strong relationships with Neurology (Professor J. Hodges), Neurosurgery (Professor J. Pickard), Stroke Medicine (Professor J-C. Baron, Dr E. Warburton), Rehabilitation (Dr S. Kirker) and Audiology (Mr D. Baguley, Mr. P. Axon, Ms. Z. Vanat) at Addenbrooke's Hospital, with the Oliver Zangwill Centre for Neuropsychological Rehabilitation (Dr J. Evans), and with the Department of Developmental Psychiatry (Professor I. Goodyer). Our work on Parkinson's Disease is a collaboration with the MRC Centre for Brain Repair (Drs. R. Barker, S. Lewis). Other collaborations include the University Departments of Experimental Psychology (Professors T. Robbins, B. Moore), Psychiatry (Professor T. Holland, Dr B. Sahakian), Anaesthesia (Professor D. Menon), and Anatomy (Drs. J. Parkinson, A. Roberts).

Project A1: Visual attention and integrated competition.

The problem of visual attention is defined by two key concepts. One is limited capacity, measured by performance decrements when a person must identify two or more things at once. Subjectively, devoting attention to one thing implies withdrawing it from others. The second is selectivity. Limited capacity requires a choice of which aspects of the input to process.

In this project, attention is conceived as a problem of biased and integrated competition in the network of cortical and subcortical brain systems that respond to visual input. These include multiple "visual areas" in occipitotemporal and occipitoparietal cortex, along with associated subcortical structures including the superior colliculus and pulvinar. Visual responses are also seen in many areas of the frontal lobe, including the frontal eye fields, premotor cortex and prefrontal cortex. The integrated competion model is based on three general principles:

(i) In many or all visually-responsive brain systems, objects in the visual input compete to be processed. Strengthened representation for one object is bought at the expense of weakened representation for others. It is this competition that gives vision its aspect of limited capacity.

(ii) In any task context, competition is biased by priming or pre-activation of cells coding currently relevant objects. Priming lends relevant objects in the visual field a competitive advantage, giving vision its aspect of top-down selectivity.

(iii) In behaviour, we interact with whole objects, whose different properties (shape, motion, egocentric location etc) and implications for action will in part be represented in different parts of the sensorimotor network. Many behavioural studies show that, to a large extent at least, objects are the "units" of attentional selection: Attending to an object makes its different properties concurrently available for report and control of action. Accordingly, competition must be integrated such that, across the sensorimotor network, the same selected objects assume dominance. In Project A3, related issues concern attention and auditory scene analysis.

In the previous funding period, the integrated competition model was developed from a broad range of behavioural, and neuropsychological results (Desimone & Duncan, 1995; Duncan, 1996; Duncan et al., 1997; Duncan, 1998; Humphreys, Duncan, & Ward, 1999). In this quinquennium, the model has been the guide for research across these levels.

A1.2 Human neuropsychology

Scientific direction: Duncan (15%)

Grant-supported posts and visitors: Rorden, Ludwig, Bonfiglioli, van Raamsdonk Students: Peers

According to the integrated competition model, objects in the visual field compete for processing over an extended period, as directly suggested by physiological data. This links the model naturally to behavioural models based on weighted parallel processing. In a collaboration with Dr C. Bundesen from Copenhagen University, we have developed one such model - Bundesen's Theory of Visual Attention (TVA) - for quantitative analysis of attentional deficits after brain damage. Correspondences can be shown between parameters of attentional function in this model and components of the integrated competition scheme (Duncan, 2001b).

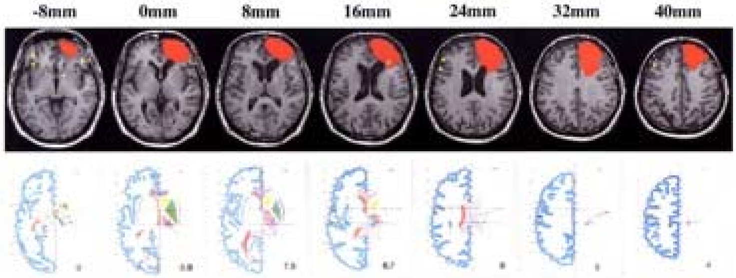
In TVA (Bundesen, 1990), objects in the visual input are concurrently processed for entry into a visual short-term memory (VSTM), from which they can be reported. For many displays, total processing rate is fixed; competition or attentional weighting determines how rapidly each separate display object is processed and hence races for VSTM access. In Bundesen's work, the model has been fit quantitatively to data from a broad range of tasks and attentional manipulations. For patient work, the most useful task is partial report (Duncan, 2001b). Brief visual displays contain mixtures of targets (to be reported) and nontargets (to be ignored). For example, participants might attempt to name just the white letters in a mixed display of white and black. By presenting targets in one or both visual fields, we can measure attentional weighting (strength of competition) for contralesional and ipsilesional sides. Clinical "extinction" (see Project A2), for example, would reflect low competitive strength on the contralesional side, and hence poor contralesional performance when there is concurrent ipsilesional material. At the same time we measure several nonspatial aspects of visual function: total processing rate across the visual field (rate of performance improvement with increasing exposure duration); capacity (number of objects) of VSTM; and top-down control or relative attentional weighting of targets and nontargets.

Our first studies, run in Birmingham with the group of Dr G. Humphreys, concerned lesions of the right inferior parietal cortex (Duncan et al., 1999). As expected in such patients, there were variable degrees of unilateral neglect assessed by standard clinical tests. Following standard accounts of neglect, the TVA analysis indeed showed a consistent attentional bias (reduced attentional weight) against the left (contralesional) field. Even more closely related to clinical neglect, however, was a bilateral reduction in total processing rate, unrelated to lateral bias. Strikingly, top-down control was entirely preserved, in both halves of the visual field. In Project A2, nonspatial aspects of neglect are also described for the auditory domain.

In a second study (Duncan et al., submitted) we used similar methods to analyze dorsal and ventral variants of classical "simultanagnosia". In simultanagnosia, the most conspicuous deficit is inability to process multiple objects in a visual display. For both variants, however, our data suggest that this is not the primary impairment. Instead, bilateral parietal lesions (dorsal variant) or left occipitotemporal lesions (ventral variant) produce a massive reduction in simple rate of uptake of visual input. Though deficits can be especially obvious with multiple-object displays, even single-object displays are equally affected with comparable measurement methods.

With the development of the Cambridge Cognitive Neuroscience Research Panel, we have gone on to analyze similar attentional parameters in a range of patient groups. Normalization of patient MRIs, using the methods of Brett, Leff, Rorden, & Ashburner (2001) (see Progress Report, Project MR3.3), allows consistent lesion description in standard brain atlas coordinates (Figure A1.2). While this work is still in progress, already it shows several unexpected results. For focal, unilateral parietal lesions, the expected spatial bias is clearly accompanied by nonspatial deficits in processing rate and VSTM capacity. These deficits are bilateral, and not associated with lesion spread into the occipital cortex. They are also seen after lesions of either hemisphere, and affect identification of both letters and faces. Evidently, parietal cortex is involved not just in spatial distribution of attention, but in the basic process of creating a conscious, reportable percept of any object in any part of the visual field. Though the results are preliminary, they also begin to suggest an intriguing dissociation between spatial and nonspatial deficits. While lateral attentional bias can follow either superior or inferior parietal lesions, and is largely predicted by lesion volume, nonspatial deficits are specifically associated with lesions of the inferior parietal lobule.

Figure A1.2. Slices from individual patient's MRI (top), transformed to standard space and re-sliced to match corresponding slices (bottom) from atlas of Talairach & Tournoux (1988). Lesion tracing in red. For comparison with this patient's lesion, yellow triangles show activation peaks from a PET study of lateral attentional bias in normal subjects.



In collaboration with Professor J. Driver (London), we have also studied patients with unilateral lesions of left or right prefrontal cortex. Once more, the spatial distribution of attention is abnormal, with some patients showing lateral bias like that of parietal patients. In line with the integrated competition view, the data suggest that any cortical lesion - occipitotemporal, parietal or frontal - can produce a global competitive imbalance against the affected side. Intriguingly, frontal and parietal lesions are also similar in their failure to affect top-down control (differential weighting of targets and nontargets). To date, indeed, we have been unable to find control deficits in any patient group, in tasks requiring spatial or nonspatial selection, and with fixed or varying target definition across trials. In terms of the integrated competition model, these results raise the question of how top-down priming signals are distributed and controlled.

A1.3 Behavioural studies

Scientific direction: Duncan (20%)

Grant-supported posts and visitors: Arnell, Bonfiglioli

In behavioural studies, temporally extended competition between visual inputs is most clearly shown by direct manipulation of temporal separation. For successive visual targets, interference extends over separations up to a half second or more, an order of magnitude greater that the predictions of conventional serial models. In the previous funding period, such measurements of "attentional dwell time" were used to address a number of issues, including competition within and between objects (Duncan et al., 1994) and within and between sensory modalities (Duncan et al., 1997). In the current period, a number of projects have used related methods to address the broader architecture of attentional competition.

In visual dwell time studies, interference is measured between visual targets presented in rapid succession. A related phenomenon, well studied in the behavioural literature, is the "psychological refractory period" (PRP); if speeded responses must be made to two successive stimuli, the second will often be delayed while the first is chosen and executed (e.g. Pashler, 1989). In classical accounts, visual competition and PRP are ascribed to quite different causes, the latter reflecting queuing in a serial response selection bottleneck (Pashler, 1989), but overlapping sources of processing limitation in these two cases have also been proposed (Jolicoeur, 1998). The debate reflects a broader issue in the study of dual task interference - the relative importance of local or domain-specific processing conflicts vs. more global attentional limitations.

To resolve the issue we have developed a new dual task method based on randomized mixing of event types within each trial (Arnell & Duncan, 2002). Auditory stimuli (e.g. simple tones) require speeded keypress responses (cf. PRP experiments), while visual stimuli (e.g. masked digits) require unspeeded identification. Randomization means that, on each trial, the two successive events can either be both auditory (conventional PRP), both visual (conventional measurement of visual dwell time), or one of each (hybrid). Certainly, such experiments can show strong double dissociations, with striking interference in both conventional cases and reduced interference in hybrids. Such results support classical models, confirming the importance of domain-specific processing conflicts. At the same time, even modest increases in task complexity can bring substantial interference even to hybrid cases. Apparently, some sources of processing conflict are so general as to cause great difficulty, for example, in identifying a visual digit while engaged in a complex, auditory stimulus-response translation. For physiological models of visual attention these results raise important questions. Though much competition may occur in classical visual areas, what is the neural basis for further, more global sources of processing conflict?

A key proposal of the competition model is integration of competitive dominance between visual areas coding different aspects of a selected object. Two further projects have extended our study of integration into new domains. In vision, input is organized in time as well as space, creating segmentation not only into objects but into discrete events. As seen for objects, we have demonstrated attentional integration within events: if a pause in a visual sequence is perceived as defining onset of a new event, it triggers a new attentional demand, while if it is perceived as a hesitation in an existing event, no new demand results (Sheppard, Duncan, Shapiro, & Hillstrom, 2002). A further question concerns spatial integration between vision and action. Our work here was inspired by the group's prior clinical work in unilateral neglect (see Project A2), showing that unseen movements of the left hand in left space can increase visual performance in the neglected left field. In a series of experiments (Bonfiglioli, Duncan, Rorden, & Kennett, 2002), we searched for similar integration in normal participants. In response to a tone, an unseen reach was planned and executed to one or the other side of space. At varying temporal intervals, visual events occurred close to left and right reach targets. At no interval, and under no reach conditions, did we observe a shift of visual attention towards the position of the reach target. This contrasts not only with the neuropsychological phenomenon but with positive results for related manipulations in young children (see Project A2). The results suggest that independence of lateral biases in vision and action may be a specific achievement of the healthy adult brain. Such independence may not be fully developed in childhood, and may potentially be compromised by brain insult.

A1.4 Functional neuroimaging

Scientific direction: Duncan (10%)

Other MRC posts: Epstein (2 years, 30%); Wojciulik (1 year, 100%)

Major themes in the functional imaging work of Duncan and Epstein are described elsewhere (frontal lobe function, Project A5; scene representation, Project A2). Here we describe preliminary experiments concerning visual attention and awareness.

In the neuropsychology of visual attention, it is generally assumed that parietal cortex has some specific and central role in attentional control (e.g. Corbetta & Shulman, 2002). In a PET study (Vandenberghe et al., 2000), we tested its role in switching from one attended location to another. Certainly we found bilateral parietal recruitment (intraparietal sulcus or IPS) when participants direct attention to a specific object in left or right hemifield. Activity was insensitive, however, to the frequency of attentional switches. A second possible control function is filtering out of visual distractors. In an fMRI study, we found bilateral IPS recruitment when an attended target letter was accompanied by irrelevant distractors; on the left, however, a similar recruitment was produced by a simple decrease in stimulus contrast. More broadly, IPS recruitment is seen with a wide range of processing demands, in domains from visual discrimination to working memory, manual or verbal response selection and problem solving (Cabeza & Nyberg, 2000). As we have documented for regions of prefrontal cortex (see Project A5), such results suggest that regional specializations within the IPS are at best relative, with no area exclusively dedicated to specific visual control functions.

One recent proposal in the literature has been that frontoparietal systems play a central role in visual awareness (e.g. Dehaene et al., 2001). In several experiments, it has been reported that attended or conscious stimuli produce strong frontoparietal responses, while unattended or unconscious stimuli do not. As participants make decisions about the stimuli they see, however, it is unclear whether this frontoparietal activity reflects awareness per se or the resultant task control operations. In a preliminary fMRI study, we asked participants simply to attend to or watch one stream of objects while ignoring another. While no immediate task was required, a surprise test of recognition memory at the end of the experiment confirmed that the instruction was obeyed. In large regions of occipitotemporal cortex, perhaps extending forward to the hippocampus, responses were stronger to attended objects. Region-of-interest analyses of frontal and parietal cortex, however, showed absolutely no response to either attended or unattended events. Though further experiments are required, these first results suggest frontoparietal involvement not in visual awareness itself, but in visual control of behaviour.

In a related theoretical project, Epstein has linked recent cognitive neuroscientific results to the phenomenological description of the stream of thought proffered by William James in the Principles of Psychology. James argued that the stream of thought consisted of relatively stable moments (substantive thoughts) connected by phases of transition (transitive "thoughts"). Epstein (2000a, 2000b) argues that the substantive thoughts -- many of which have an imagistic content -- may reflect momentarily stable patterns of neural firing in perceptual processing regions of the brain such as the ventral visual stream. In contrast, the transitions between thoughts may be mediated by two mechanisms: a medial temporal lobe memory mechanism that supports a network of possible associations, and a frontal control mechanism that ensures that the direction of thought remains consistent with current behavioral goals. James' scheme is particularly interesting when considered in the light of the above neuroimaging studies linking activity in occipitotemporal and frontal-parietal regions to visual awareness and task control.

Project A2: Spatial representation and impairment.

This project has considered normal and pathological representation of space and the body. This includes between-modality and sensorimotor integration, spatial frames of reference, imagery, and the influence of attention on perception and action. A primary clinical focus has been on unilateral spatial neglect, a disorder that is associated with slowed recovery, poor response to rehabilitation and impoverished outcomes. In parallel with theoretical development, understanding the factors that may lead to chronicity and the investigation of ameliorative techniques have been central to these studies.

A2.1 Interactions of vision and action

Scientific direction: Robertson (2 years, 20%), Manly (10%)

Grant-supported scientists and visitors: Mattingley

Students: Dobler

In prior work, Robertson had shown how left-sided visual neglect in stroke is strongly affected by action programming and context. An example is the demonstration that left visual neglect can be alleviated by concurrent activity of the left hand - specifically if the movements occur within left space defined relative to the midline. This modulation of spatial attention appears to occur whether or not the hand can be seen by the patient and whether or not the activity is directed towards the current spatial task. In the current funding period, we have shown the positive clinical effects of encouraging patients to make such movements during everyday activities (Robertson, Hogg, & McMillan, 1998a; Wilson, Manly, Coyle, & Robertson, 2000). Modulation also occurs within the much tighter time-frame of computerised extinction measures (Mattingley, Robertson, & Driver, 1998). Replication and extension of these findings is now also taking place internationally (e.g. Frassinetti, Rossi, & Ladavas, 2001; Brown, Walker, Gray, & Findlay, 1999; Gainotti, Perri, & Cappa, 2002; Samuel et al., 2000). Dissemination of these and other therapeutic findings with neglect to the clinical as well as to the scientific community has been a strong aspect of this work (Manly, 2001; Manly, 2002; Manly, in press; Manly & Mattingley, in press; Manly & Robertson, in press; Manly, Ward, & Robertson, 2002b; Robertson, 1998a; Robertson, 1998b; Robertson, 1999a; Robertson, 1999b; Robertson, 1999c; Robertson, 2000; Robertson, 2001; Robertson, in press; Robertson & Halligan, 1999; Robertson & Hawkins, 1999; Robertson & Manly, 1999)

Although the clinical results are clearly suggestive of a high level interaction between movement planning/execution and the allocation of visual attention - as envisaged in the integrated competition model (see Project A1) - the precise mechanisms underpinning these effects remain unclear. One puzzling aspect is that intensive investigation with healthy adults has shown no hint of such a relationship (Bonfiglioli et al., 2002). Our recent work has, however, illustrated reliable effects of concurrent limb activity on visual attention in healthy young children (below the age of 9) - even on purely perceptual tasks (Dobler et al., 2001a). This is consistent with a process linking spatial attention and movement in development that becomes masked in maturity but which may be uncovered by acquired brain damage in adulthood. Further investigations are currently underway with children - in parallel with adults showing neglect - to further delineate this relationship. The findings also raises potentially important questions about reciprocal effects of impairment in movement or attention in development (see below).

A2.2 Spatial bias and non-spatial control functions

Scientific direction: Robertson (2 years, 20%), Manly (20%)

Grant-supported scientists and visitors: Rorden, Mattingley

Students: Dobler

Although unilateral neglect is observed with almost equal frequency immediately following left- and right-hemisphere stroke, there is a striking asymmetry in patterns of recovery with almost all chronic patients having right hemisphere damage and neglecting left space. Accordingly, it has been proposed that concurrent damage to other right hemisphere dominant systems might form the setting conditions that allow the spatial bias to persist (see A3 Proposal for more detailed account). In line with this view, we have shown that co-occurring deficits in non-spatial sustained attention (a capacity predominantly linked with the right hemisphere in neuropsychological and functional imaging studies) are indeed associated with persistent forms of the disorder (Robertson et al., 1997b). More compellingly, we have shown a direct modulatory effect of external alerting on spatial awareness among right hemisphere neglect patients (Robertson et al., 1998b). Continuing the theme of more general control functions, work with Dr N. Lavie (London) has demonstrated that awareness of information within the neglected field (in this case, distracting information) could be reduced by increasing the attentional demands of a task completed at fixation (Lavie & Robertson, 2001). Finally, we have shown a heightened tendency for patients to become caught-up in perseverative responses to ipsilesional stimuli, and further shown these to be strongly determined by the presence of response relevant but neglected contralesional information (Manly, Woldt, Watson, & Warburton, 2002c).

We have developed an argument that this relationship between spatial bias and non-spatial attentional limitations may also apply to children. In 1997, we reported on the case of a 10-year old boy who, despite above-average intellectual abilities and the absence of any clear etiological event or brain abnormality, showed a striking and persistent tendency to neglect information in left space (Manly et al., 1997). Our investigations of his non-spatial attentional function - which led to our development of the Test of Everyday Attention for Children (TEA-Ch), now a widely used clinical measure (Manly et al., 2002a) - revealed significant deficits in sustained attention. Subsequent investigations screening children for poor non-spatial sustained attention have confirmed this association within the normal school age population and in children diagnosed with attention deficit hyperactivity disorder (Dobler, Manly, Anker, Robertson, & Atkinson, submitted-a). Again, the parallels between these interactions in development and in the injured adult brain offer the prospect of a more complete life-span theoretical treatment. Current investigation concerns clinical implications of these results, including potential amelioration of spatial biases in children (which our research suggests may be relatively common), and interactions with motor and attentional functions.

A2.3 Non-visual spatial representation and cross-modal interaction.

Scientific direction: Robertson (20%, 2 years)

Grant-supported scientists and visitors: Mattingley, Rorden, Farrell

Detailed single case experimental designs have demonstrated the integration of spatial attention across sensory modalities and helped illuminate attentional effects in apparently primary sensory impairment. In the context of impaired left-sided sensation following right hemisphere lesion, for example, we have shown facilitation of tactile awareness when a visual cue is simultaneously presented at a proximal location (Rorden, Heutink, Greenfield, & Robertson, 1999). In contrast, when tactile and visual stimuli are simultaneously presented within ipsi- and contralateral space, a competitive cross-modal extinction effect is observed (Mattingley et al., 1997).

A further important aspect of parietal function lies in updating of the body's location in external space. In an initial study, participants were rotated with vision occluded, and then asked to point towards previously seen objects within a fixed spatial array. When updating their position in line with the experienced rotation, neurologically healthy volunteers show no effect of the extent of rotation in their response times. If however, they are asked to point to the objects as if no rotation had occurred, the proportionate relationship between reaction time and degree of rotation suggests mental rotation back to the starting position (Farrell & Robertson, 1998). In contrast, patients with right posterior damage showed no evidence of such automatic updating (Farrell & Robertson, 2000). Further work has examined spatial updating in locomotion (Farrell, Robertson, & Thomson, in press). Given the co-occurrence of visual neglect with basic sensory loss, demonstration of higher level representational deficits can be difficult. This work, in focusing on processes that can operate independently of vision, offers important theoretical and clinical advances in understanding normal and pathological function.

Unilateral neglect can operate within different spatial frames of reference (e.g. Driver & Halligan, 1991; Halligan & Marshall, 1991). However, most clinical assessment relies exclusively on visual tasks performed within extrapersonal space. Work has continued to develop improved assessment techniques, including assessment of neglect for the body (Beschin & Robertson, 1997; McIntosh, Brodie, Beschin, & Robertson, 2000) and practical means of dissociating attentional from basic perceptual factors (Edgworth, Robertson, & MacMillan, 1998).

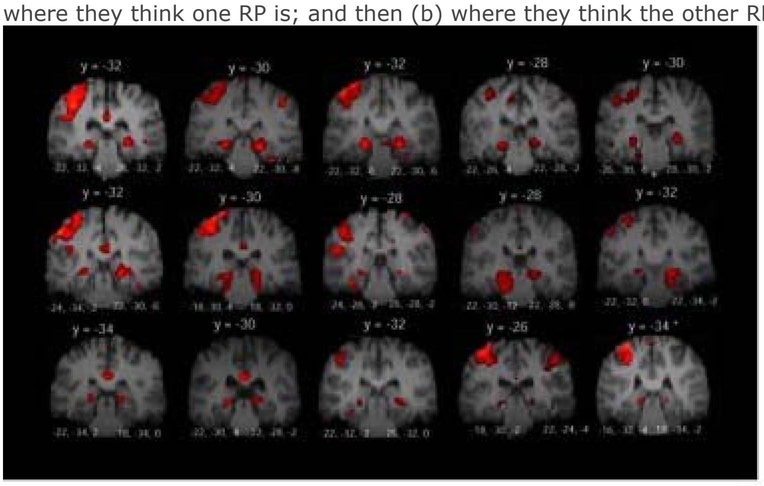
A2.4 Frames of reference, perceptual input, and imagery

Scientific direction: Marcel (10%)

Grant supported posts and visitors: Dobel

Any spatial representation is with regard to a particular frame of reference. In normal sensory perception a number of representations are computed differing in reference frame, supposedly starting from one that is based on receptor surface, eg. retinotopic, eventually encompassing egocentric, and possibly geocentric, allocentric, object-centred and body-centred. A powerful confusion error of self-location has been discovered where people lose the appropriate egocentric frame of reference (Marcel & Dobel, in press). If people are blindfolded and asked to point to two previously located reference points on the walls of the room they are in, in most subjects the angle between the arms reflects the axes of symmetry relating the relevant walls (i.e. 180 or 90 degrees, depending on whether points are located on opposite or adjacent walls), an answer which neglects the person's own position relative to the reference points (see Figure A2.1). When asked why, subjects justify their answer by logical necessity ("It must be: they're opposite each other/in adjacent walls"). This persists even when subjects know that they are not near the room's axes of symmetry. The same behaviour happens when people are asked to imagine the situation. The conditions under which this phenomenon occurs and is prevented suggest that being in perceptual contact with a structured perceptual world maintains a normally dominant egocentric reference frame, and that this obtains irrespective of whichever sensory modality is operative, certainly vision and touch. Deprived of such perceptual contact (eg. by being blindfolded, losing a sensory modality, engaging in imagery, absence of perceivable environmental structure), people are subject to delusions of self-location, i.e. their location in relation to features of the environment, whereby structural descriptions of their body and their environment are mistakenly defaulted to and relied on. Work on blindsight (Marcel, 1998; Weiskrantz, 1986) suggests that this effect of perceptual contact does not rely on conscious perception, since people with blindsight are able to point to and grasp objects displayed in the blind field, which relies on an egocentric reference frame.

Figure A2.1 Room showing reference points (RPs) and axes of symmetry.Blindfolded subjects point to (a) where they think one RP is; and then (b) where they think the other RP is.



A2.5 Somatic attention: neglect, vision, and frame of reference

Scientific direction: Marcel (20%)

Other MRC posts: Cox (80%), Gillmeister (80%), Postma (80%) (1 year each)

Grant-supported posts and visitors: Rorden

Several lines of research have been pursued and new ones opened up in the area of somatic attention. We aimed to develop a differential diagnostic test for somatic neglect. Current tests either (a) use grasping of the affected limb by the intact one, and thus rely on motor performance and external spatial representation of the body, or (b) use detection of single or bilateral tactile stimuli, and thus cannot distinguish neglect from hemianaesthesia or extinction. We sought to use the influence of undetected tactile stimuli to the affected side of the body on performance related to the intact side. Adapting methods from Driver and Grossenbacher (1996), we studied interference from tactile stimuli on the affected hand on speeded tactile discrimination on the attended intact hand. Assessment of validity and generality in patients with neglect and hemisomaesthesia and control patients is being conducted in collaboration with Dr E. Ládavas (Bologna).

A set of experiments using this procedure with normal subjects has shown that a proportion of neurologically intact people show persistent experiential mislocation of salient stimuli from the unattended hand to the attended hand. The proportion showing this is similar to that of parietal patients showing allochiria (experiential displacement of stimuli or sensations from contralesional to ipsilesional locations). Our data suggest two things. (a) At least some neglect and extinction is due not to unawareness of the affected stimuli but to awareness of them at locations occupied by stimuli on the intact side of space. This is consistent with recent finding in neglect patients (see A2.2) that perseverative cancellation of targets on the right is reduced by removal of targets on the left. (b) Since an appropriate proportion of normal people show similar allochiric phenomena, such effects in patients may be due to individual differences in premorbid susceptibility. In recently completed and ongoing experiments we have shown that such effects are underlain in relevant subjects by fusion of bilateral tactile stimuli analogous to auditory phenomena (the first observation of tactile fusion). We are currently investigating the extent to which this individual difference is transmodal or modality-specific, by assessing whether the relevant individuals show an equivalent differential tendency to fusion effects in vision and audition. We are also investigating whether such fusion is affected by tactile "streaming". We are doing so by studying (a) effects of a/synchrony of fusing stimuli, and (b) whether the unattended stimulus can be captured into and kept in a separate stream by presentation of a preceding and following sequence of stimuli on that side.

Using the same procedure of tactile discrimination on one hand with congruent, incongruent or no stimuli on the other, we have partially replicated and extended Driver and Grossenbacher's study to assess the effects on distraction and interference of orientation of head and eyes to the attended versus unattended hand and that of vision of these body parts (eyes open or shut). In Driver and Grossenbacher's study seeing one or other hand had no effect, while orientation toward the attended or unattended hand interacted with hand separation. In contrast, in our study seeing one or other hand produced a significant interaction with interference, while head and eye orientation per se to either hand was ineffective. Thus, differential orientation with eyes closed was without effect. However, seeing the attended hand led to least distraction from unattended stimuli and least interference from incongruent stimuli, while seeing the unattended hand led to most distraction and most interference. It appears that seeing a body part increases the dominance of tactile stimuli on that body part for attention (consistent with Kennett, Taylor-Clarke & Haggard, 2001), while orientation per se does not. We intend to disentangle whether these effects are due to vision of the location or of the body part itself by manipulating visual perception of a video monitor per se in the location of the stimulated body part or of that bodypart displayed on the monitor either in its appropriate location or in other locations (see Proposals, A4.6). We have used this procedure to investigate the involvement of different spatial frames of reference in somatic attention and interference. While the subject makes speeded discriminations of tactile stimuli on one hand or other body part, simultaneous stimuli (congruent or incongruent) are presented on another bodypart that is (a) contralaterally homologous or not, (b) on the same or opposite side of the body, or at varying distances either (c) in external space or (d) in somatic space. The last two factors were manipulated independently by varying arm and leg positions. Somatic distance (e.g. target: hand; distraction: ipsilateral arm, foot, contralateral arm, hand, foot) and same/different side had no effect on interference and produced no interaction. External distance had a small but inconsistent effect, but the major interference was from the contralaterally homologous body part. The fact that somatic homology and external distance did not interact is consistent with their affecting different levels. However, whether frames of reference interact in attention may depend on whether they are integrated, and which reference frames have to be integrated ought to depend on the nature of the task. An itch can be somatically located without dispositional proprioception (e.g. by IW who lacks proprioception, see project A4.3), but scratching it requires knowing its external location.

A2.6 Phenomenal and functional aspects of imagery for manual posture

Scientific direction: Marcel (15%)

Other MRC posts: Cox (20%), Gillmeister (10%) (1 year each)

We have addressed a different aspect of spatial representation of the body and its relation to neglect by investigating identification of left/right hands displayed visually at various orientations. In normal subjects latency was affected by orientation, the longest being to depiction of the most mechanically difficult posture, and immobilising one hand delayed identification selectively to depictions of that hand, suggesting the role of kinaesthetic or motor imagery. In collaboration with Drs Bisiach, Nico, Antonucci and Pizzamiglio in Italy, we used this procedure with patients with right hemisphere lesions with and without neglect and with and without unilateral plegia and loss of sensation, also investigating the effect of immobilising the intact hand to assess whether representation of the affected hand can be employed. The results indicate that patients with unilateral somatic neglect, but not those with severe unilateral motor or sensory loss, can perform the task and are able to manipulate imagery of their affected hand (i.e. when the other hand is immobilised) even when they are not conscious of proprioception. However, patients with neglect are selectively unable to use visual or kinaesthetic imagery of their affected hand to identify the orientation that is most difficult to achieve mechanically. These data suggest a dissociation of phenomenal and functional aspects of somatic imagery and suggest that neglect has a particular effect on kinesthetic spatial imagery.

A2.7 Auditory aspects of unilateral neglect

Scientific direction: Carlyon (10%), Cusack (15%), Robertson (5%)

Taking advantage of the expertise on auditory processing at the Unit, neglect patients' abnormalities in auditory attention have also been examined. Cusack, Carlyon and Robertson (2000) found that right hemisphere patients, diagnosed with neglect on the basis of performance on visual tasks, showed a curious attentional deficit in auditory processing - even when judgements were made exclusively on sounds presented to the midline. When asked to judge whether a tone's frequency was modulated (a 'warble' sound) or fixed, the patients performed as well as controls. When, however, the judgement was of relative pitch of two sounds separated by a brief interval, patients were grossly impaired. As the frequency judgement was directly equivalent in the two cases (and total duration was controlled), the impairment suggests a deficit in making "between object" comparisons. The defect was not specific to changes in frequency; patients were impaired at judging which of three sounds, presented close to midline, occupied a different location from the other two, but were intact at judging the location of single sounds. Once more, conclusions are reminiscent of object-based models of visual attention, and the integrated competition view (Project A1). In this case, however, the distribution of information is temporal rather than spatial - and further indicates the association between the neglect syndrome and much more widespread attentional impairment.

As with vision, examination of auditory attentional deficits may be contaminated by co-existing perceptual loss. Using noise burst stimuli with variable inter-aural delays (which perceptually have the effect of locating the sound more to one side of space than the other) the point of subjective midline was calculated for RH patients with neglect and hearing/age matched controls. In contrast to some other studies on the topic, no consistent bias towards hearing sounds as originating within right space was observed (Cusack, Carlyon, & Robertson, 2001). However, attentional effects associated with a sound's perceived origin within left space have been demonstrated. When healthy participants are exposed to a repeating sequence of tones (low high low - low high low) - and depending on the precise frequency difference between the tones - they will generally initially experience the sequence as a single "galloping" rhythm. Over time, however, the sequence tends to become separated into two "streams" - a repeating low tone pattern and a repeating high tone pattern. By presenting the sequence monaurally to healthy subjects and manipulating the presence of a distractor task at the other ear, Carlyon et al. were able to demonstrate the modulatory effects of attention on the segregation process (see Project A3). Consistent with this view, right hemisphere patients showed markedly different segregation functions in streams presented to the left ear in comparison to those presented to the right - which did not differ from those of controls (Carlyon, Cusack, Foxton, & Robertson, 2001). This finding invalidates models of auditory streaming based solely on brainstem processes (Beauvois and Meddis, 1991), and suggests that neglect patients may perceive complex auditory sequences (such as mixtures of two voices) differently when the talkers are on the left than when they are on the right.

A2.8 Scene representation

Scientific direction: Epstein (2 years, 70%)

Epstein has been pursuing studies of the cortical basis of navigationally-relevant spatial representations in humans. In earlier work, he demonstrated the existence of a region in parahippocampal cortex (the "parahippocampal place area", or PPA) that responded preferentially in fMRI to stimuli that convey information about the spatial structure of surrounding space (i.e. visual scenes). In a neuropsychological follow-up (Epstein et al., 2001) he demonstrated that patients with damage to this region exhibit profound difficulties in learning new environments. Furthermore, they exhibit a visual learning deficit that is specific for scene-like but not object-like stimuli, a result that was predicted from the fMRI data. Subsequent studies performed in collaboration with Dr Kim Graham and the staff of the fMRIB Centre in Oxford examined whether this region supported egocentric (observer-centered) or allocentric (world-centered) spatial representations (Epstein, Graham & Downing, submitted). An event-related adaptation paradigm was used in which fMRI response was measured in the PPA while subjects viewed events consisting of the sequential presentation of two photographs of tabletop scenes. The photographs could either depict entirely different scenes, the same scene from different viewpoints, or the same scene containing different objects. Strikingly, the response in the viewpoint change condition was exactly equivalent to the response in the different-scene condition (and significantly higher than the response in the object-change condition). These results demonstrate that the PPA considers two photographs of the same spatial layout taken from different viewpoints to be as representationally distinct as two photographs depicting entirely different tabletop layouts, and suggest that the PPA represents space in egocentric (viewer-centered) coordinates. These results provide an interesting contrast to neurophysiological studies from the rat indicating that the hippocampus supports an allocentric representation of space (the cognitive map of O'Keefe and Nadel, 1978) and argue for an entirely distinct spatial map in the PPA.

Project A3: Auditory scene analysis and the perceptual representation of sound.

When someone is faced with the task of attending to a single voice in the presence of a competing talker, they must perform a number of highly sophisticated operations. The most important of these may be summarised as follows: (i) At any one time, the outputs of the early frequency analyses performed in the two inner ears must be "parsed", so that the frequency components arising from each voice are grouped together, and are segregated from those of the other voice, (ii) the target voice must be tracked over time, (iii) decisions must be made on how to interpret "missing data", such as when part of the speech is masked by an extraneous noise, (iv) the target voice must be selected (by attentional mechanisms) for further processing, and (v) linguistic analyses must be performed on the selected voice. The first three in the list can be collectively termed "auditory scene analysis" or ASA (Bregman, 1990), and are in many ways analogous to segregation of visual input into discrete objects, a basic aspect of object-based attentional theories (Project A1). Traditionally, the different auditory processes have been studied largely in isolation, and, in particular, ASA is commonly studied separately from attentional and linguistic analyses. Furthermore, with few exceptions, the ASA studies have typically relied on behavioural measures obtained with very simple stimuli played to normal subjects. Although this approach has produced a wealth of evidence on the stimulus parameters that the brain can and cannot exploit when analysing an auditory scene, it has provided little information on the neural bases for this analysis, nor on its relationship to more cognitive processes. Our strategy has been to bridge this gap using the wide range of techniques and subject populations that are available at the CBU and elsewhere in Cambridge. In doing so, we have aimed to provide new insights not just into ASA, but also into higher-level cognitive processes. In addition to behavioral studies of scene analysis which have incorporated attentional and speech tasks, the neural bases of selective auditory processing have been studied using EEG (with Pulvermüller) and fMRI (Johnsrude). Further insights were obtained by testing stroke patients suffering from unilateral neglect (with Robertson), and deaf patients fitted with a cochlear implant (with Baguley and colleagues at Addenbrooke's hospital).

A3.1 Auditory streaming and attention

Scientific direction: Carlyon (15%), Cusack (15%)

Other MRC posts: Deeks (30%)

A simple view of the relationship between ASA and attention is that low-level mechanisms automatically parse the acoustic input into auditory objects, which are then selected by higher-level and entirely separate attentional processes. However, we have shown that attention is crucial for one aspect of ASA, namely the build-up of "auditory streaming". Carlyon, Cusack, Foxton, and Robertson (2001a) presented normal listeners with a sequence of tones of frequencies A and B, in a series of repeating triplets "ABA-ABA-ABA…" (the dashes represent silent intervals). When the frequencies of A and B are similar, or the presentation rate is slow, subjects typically report hearing all the tones in a single auditory stream, with a galloping rhythm. In contrast, when the A and B frequencies are far apart, and/or the presentation rate is fast, the "A" and "B" tones stream apart, and the percept of the galloping rhythm is lost. This paradigm measures a phenomenon that is widely used by composers of polyphonic music, and which forms the basis of our ability to track one speaker in the presence of interfering speech. In the Carlyon et al. (2001a) study, we exploited another aspect of the phenomenon, which is that the tendency to hear two streams builds up during the sequence. We presented a 20-sec. sequence to one ear and, in condition 1, asked subjects to continually judge the number of streams heard. As expected, the number of "two stream" judgements increased over time. In a second condition, we asked subjects to perform a competing task on a sequence of noises presented to their other ear during the first 10 sec of the tone sequence, after which time they were required to switch attention to the tones and to start making the streaming judgements about the last 10 sec. The key finding was that the proportion of "two stream" judgements made shortly after the switch was similar to the proportion at the beginning of the sequence in condition 1, and much lower than that observed after 10 sec in that condition. Hence, by manipulating attention during the first half of a sequence, we affected streaming during the second half. A second experiment showed that performing a competing task on the same sequences as those on which streaming judgements were to be made did not reduce the build-up. Combined with our recent finding (Cusack, Deeks, Aikman, & Carlyon, submitted) that build-up is reduced by a competing task performed on different sounds presented to the same ear as the target stream, this indicates that the build up of streaming depends on whether one attends to a particular auditory object, rather than on whether one performs a particular task or attends to a spatial location. An additional finding is that the build-up of streaming can be inhibited by a visual competing task, providing evidence for a supra-modal attentional limitation (c.f. Arnell & Jolicoeur, 1999). Further evidence for a supra-modal attentional influence on ASA came from streaming judgements of sequences presented to the left and right ears of patients suffering from unilateral neglect of stimuli on the left side of space, as diagnosed on the basis of visual tasks (see Project A2). These patients showed less streaming of sequences presented to their left ears than of sequences presented to their right ears, or to either ear of controls. Finally, we have shown that, if streaming is allowed to build up, then it can be largely abolished by either turning the sequence off for a few seconds, or, equally, by requiring subjects to perform a competing task for a few seconds. This is consistent with the idea that the act of switching attention may "reset" the streaming mechanism.

It should be stressed that the conclusion that the build-up of auditory streaming is dependent on attention does not necessarily apply to other aspects of ASA. Indeed, our finding that attending to a competing stimulus can inhibit the build-up is consistent with that stimulus having been segregated from the tone sequence by pre-attentive mechanisms. We have suggested (Carlyon et al., 2001a) that perceptual segregation of sounds that start and stop at different times ("grouping by common onset") is one such pre-attentive form of ASA.

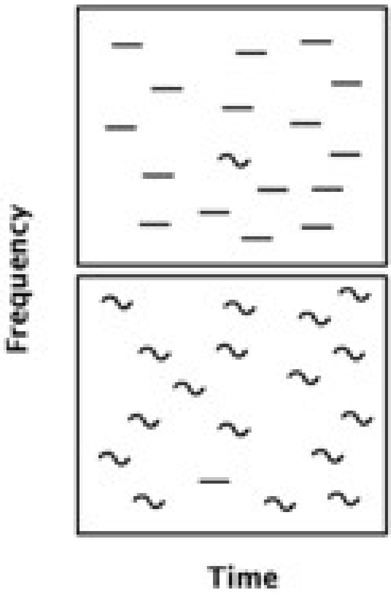
A3.2 Perceptual asymmetries

Scientific direction: Cusack (15%), Carlyon (7.5%)

In the visual modality, striking perceptual asymmetries are observed when a subject is required to select a target from a background of distracting stimuli. For example, the time taken to identify a "Q" against a background of "O"s is substantially faster than that taken to identify an "O" against a background of "Q"s. One of the first explanations, which is still extremely influential (Triesman & Gormican, 1988), asserted that early in visual processing, we form a number of separate feature maps. If the target uniquely contains a feature, such as the straight line that forms the tail of a "Q", then the entire array of detectors for this feature may be examined in parallel. Conversely, if the target is defined by the absence of a feature, then the task is much harder, and a serial search is required. Although the precise mechanisms underlying these asymmetries are still the subject of some debate, it remains true that the presence or absence of visual features can have a strong effect on performance. In contrast, there has been little research on the presence or absence of features, or indeed any evidence for perceptual asymmetries, in the auditory domain.

Using an analogue of visual search tasks, we have provided evidence that frequency modulation ("FM") is an auditory feature (Cusack and Carlyon, in press). In one experiment, we presented subjects with a sequence of tones that were quasi-randomly distributed in time and frequency. In one condition (Fig A3.1, top), a single modulated target was presented (on 50% of trials) against a background of steady tones, and subjects were asked to report whether a "wobbling" tone was present. Performance in this condition was substantially better than when the non-targets were FM tones and subjects had to detect a single steady tone (Fig. A3.1, bottom). Furthermore, we obtained an analogous pattern of results using a different manipulation, in which subjects were better at detecting a long-duration tone against a background of shorter tones than vice versa. This is consistent with evidence from the visual modality of better detection for a stimulus with "more of" a feature against a background of stimuli containing "less of" that feature (e.g. a long line against a background of shorter lines) than vice versa (Beck, 1982).

Figure A3.1



A3.3 Effects of attention and grouping in auditory cortex

Scientific direction: Cusack (15%), Carlyon (7.5%), Johnsrude (5%)

We have used fMRI to investigate the effects of auditory grouping and attention on activation of auditory cortex (Cusack, Carlyon, Johnsrude, & Epstein, 2001). We either presented a single sequence of tones heard towards the left or right, or two interleaved sequences, one heard on each side. The tones could be made to appear on one side either by presenting them to one ear only, or by presenting them binaurally such that they lagged slightly in one ear; this caused them to be heard on the non-lagging side. Subjects were instructed to detect a rising pattern of tones on either the left or right side of the head. The task instructions had no effect on the relative amount of activation on the left or right side. However, greater activation was found for two monotic sequences that alternated between the ears than for a single binaural sequence, even though in these two conditions the total amount of energy presented to each ear was identical. One interpretation of this finding, which we intend to pursue in the next quinquennium, is that activation of auditory cortex is modified by the number of "auditory objects" perceived, which was greater in the "alternating between ears" than in the binaural condition. If so, then the fact that these effects can be measured in auditory cortex would confirm our interpretation of one of our behavioural streaming experiments, which is that grouping by common onset occurs at an early, pre-attentive stage of auditory processing (see above).

A3.4 The continuity illusion

Scientific direction: Carlyon (20%), Pulvermüller (5%)

Other MRC posts: Deeks (40%), Shtyrov (5%)

CBU collaborators: Norris, Butterfield, Hauk

Grant-supported scientists and visitors: Micheyl

When a sound is turned off briefly and then on again, it can be perceived as continuous when the silent gap is filled by an "inducing" sound, such as a burst of noise. This "continuity illusion" only occurs if the frequency content and timing of the noise is such that it could have plausibly masked the sound had it remained uninterrupted. It is important for the perception of stimuli such as speech in noisy environments; for example, if a sound such as /i/ is masked mid-way through by a brief sound, it would not make sense to interpret it as two separate phonemes separated by a gap. Most previous studies of the illusion have relied solely on subjective reports, which, we have argued (Carlyon, Deeks, Norris, & Butterfield, 2002a), do not distinguish even between broad classes of explanation for the effect. For example, if a subject reports a tone interrupted by a noise as being continuous, then at least two explanations are possible. At one extreme, s/he could reason that the tone ended at particular time and frequency, reappeared later at the same frequency, and conclude that it "must have" continued behind the noise. At the opposite extreme, it could be that, during the illusion, the firing pattern of neurons, perhaps at a fairly peripheral stage of auditory processing, resembles that which would have occurred had the "inducee" been physically present. We performed two studies, both of which imposed constraints on the possible level of processing at which the effect occurs.

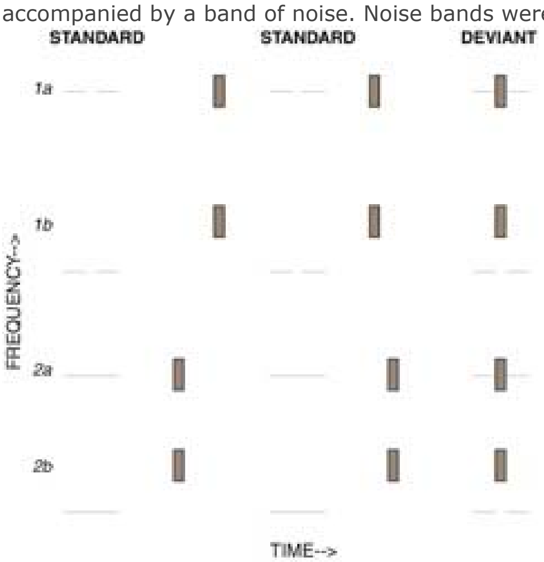
A3.4.1 Influence on vowel identification

We have shown that the mechanisms responsible for the continuity illusion "feed into" those involved in vowel identification (Carlyon et al., 2002a). Subjects were required to identify a two-formant vowel under a number of conditions. When the formants were presented simultaneously and pulsed on and off together, identification was very good, but became poor when the formants were alternated in time. In the most important condition, the formants were alternated, but the gaps in the upper formant were filled with high-frequency noise, and those in the lower formant region were filled with low-frequency noise. This caused the formants to be perceived as continuous and hence as simultaneous with each other, and led to a substantial increase in performance. This finding not only provided a performance measure of the illusion, inconsistent with "cognitive re-interpretation" explanations, but also showed that accurate vowel identification does not require formants to be physically simultaneous.

A3.4.2 An electrophysiological correlate of the continuity illusion

We have recently obtained a neurophysiological measure of the continuity illusion (Micheyl et al., in press). The mismatch negativity (MMN) is a negative deviation in the EEG response to a rare "deviant" sound presented in a sequence of more frequent "standards". It can be obtained when subjects are instructed to ignore the sounds and to attend instead to a visual stimulus – which, in our study, was a silent video. We measured the MMN to a deviant that consisted of an interrupted tone in which the silent gap was filled either with an "on frequency" noise, which induced the illusion of continuity, or with an "off frequency noise", which did not. When the standards consisted of continuous tones the MMN was larger when the deviant was perceived as interrupted (off-frequency noise; condition 2b, Fig. A3.2) than when it was heard as continuous (on-frequency noise, condition 2a). Conversely, when we used interrupted tones as standards, the MMN was larger when the deviants were perceived as continuous (on-frequency noise, condition 1a) than when heard as interrupted (off-frequency noise, condition 1b). Note that, by measuring an interaction between standard and deviant type, the study controlled for any "coincidental" differences between ability of particular standards or deviants to elicit MMNs. Hence we have demonstrated that the continuity illusion can be observed objectively in a situation where subjects do not focus attention on the sounds, and where no response is required. Furthermore, the latency (<240 ms) and neural locus (around auditory cortex) of the MMN provide strong evidence against "late re-interpretation" explanations for the phenomenon.

Figure A3.2 Subjects heard a sequence consisting of common (80%)"standard" tones (two shown for each condition) and rare (20%) "deviants" (one shown per condition). Each deviant was an interrupted tone accompanied by a band of noise. Noise bands were also interspersed between the tones.



A3.5 ASA by cochlear implant users

Scientific direction: Carlyon (20%)

Other MRC posts: Deeks (15%)

Grant-supported scientists and visitors: Long

The cochlear implant is the first ever successful sensory-neural prosthesis. We have recently developed the technical capability and clinical contacts to study ASA in implant users in association with colleagues at Addenbrooke's hospital, Cambridge, as well as continuing experiments with overseas collaborators (C. McKay and H. McDermott in Australia, J. Wouters and A. van Wieringen in Belgium). These experiments allow us to address a clinically important question, while permitting attacks on basic scientific issues that are impenetrable with normal, acoustic stimulation.

The clinical issue arises from the fact that implant users can often understand speech in quiet, but have great difficulty in noisy situations. An example of a basic scientific issue is the extent to which listeners can use purely temporal information to segregate concurrent sounds. In normal hearing, sounds of different frequencies produce different temporal patterns of firing in the auditory nerve, but usually also excite different neural populations. Hence, if a subject can hear one sound in the presence of the other, it is hard to tell whether s/he is using the temporal or the place-of-excitation information to do so. In an implant, however, one can easily separate the temporal and place-of-excitation factors. This is possible because the implant consists of an array of electrodes distributed along the length of the cochlea, so one can vary place-of-excitation by manipulating which electrode(s) is stimulated, and manipulate temporal cues by, for example, selecting a single electrode channel and varying the temporal pattern of impulses applied to that channel. We have played mixtures of regular pulse trains to a single channel, and determined whether cochlear implantees can hear the two underlying pitches, or whether they hear a single, undifferentiated pitch. The results show that, when a pulse train of a given "carrier" frequency is modulated at a much slower rate, patients can indeed extract the pitches corresponding to both the carrier and modulation rates (McKay & Carlyon, 1999). This is the sort of pattern that occurs in the outputs of modern cochlear-implant speech-processing schemes, such as the widely used "continuous interleaved sampling" algorithm, when presented with a single voice; the modulation rate corresponds to the voice pitch and the carrier rate is fixed. However, when two harmonically unrelated pulse trains are mixed, patients hear a single, somewhat rough, pitch, corresponding to the rate of the higher-rate pulse train (Carlyon, van Wieringen, Long, Deeks, & Wouters, 2002b; Long, Carlyon, McKay, & Vanat, 2001; van Wieringen, Carlyon, Long, & Wouters, 2002). We have shown that these results, as well as those obtained with our acoustic simulations of cochlear implant hearing (see below), can be captured by a simple model of pitch perception; this model also accounts for a range of findings that are inconsistent with the most popular "autocorrelation" class of pitch models. The findings and the model indicate that a) current cochlear implant processing strategies do not allow users to exploit pitch differences between different voices to segregate them from each other, and b) neither implantees nor normal listeners can use purely temporal information to segregate concurrent sounds, in the absence of the "place of excitation" cues that are produced by pitch differences.

We have also investigated whether implant patients are sensitive to another class of potential ASA cues, arising from differences in the temporal pattern of stimulation on different electrodes (Carlyon, Geurts, & Wouters, 2000). If patients could use these cues, this might allow them, for example, to segregate one formant of one speaker's voice from a different formant of another voice. We showed that patients could sometimes detect very small (<100μsec) delays between two pulse trains applied to different electrodes that stimulated quite different populations of auditory nerve fibres. However, performance on this task was quite variable and depended idiosyncratically on which electrode was delayed, suggesting that these small asynchronies are unlikely to provide a firm basis for sound segregation. Importantly, though, it was unaffected by the presentation of another pattern of stimulation on an intermediate electrode, when this stimulation started 400 ms before, and ended 400 ms after, that on the two electrodes to be compared. We attributed patients' resilience to this potentially interfering stimulation to the fact that the onset and offset asynchrony caused it to fall into a separate "auditory stream" from that on the target electrodes. We will be further testing this interpretation in the next quinqennium; if verified, it will be the first demonstration of the perceptual segregation of concurrent stimuli by cochlear implant users.

Finally, in parallel with our experiments with implant users, we have developed an acoustic approximation to electrical stimulation that can be used with normally hearing listeners. By bandpass filtering acoustic pulse trains in a frequency region that is high relative to the repetition rate of that train, it is possible to vary the temporal patterns of stimulation without giving rise to cues based on the place of excitation on the basilar membrane. This produces results very similar to those obtained by manipulating the temporal parameters of a pulse train applied to a single channel of a cochlear implant (Carlyon et al., 2002b; Long et al., 2001; McKay & Carlyon, 1999; van Wieringen et al., 2002). It allows us and other experimenters to pilot implant experiments with a homogenous and readily-available population of normal listeners. Perhaps more importantly, it adds power to our experiments by excluding alternative explanations that are specific either to acoustic or electrical stimulation.

A3.6 Psychoacoustics of fundamental basic auditory processes, and applications to special populations

Scientific direction: Carlyon (20%)

Other MRC posts: Deeks (15%)

Grant-supported posts and visitors: Gockel, Micheyl, Lyzenga

Carlyon's research into more basic auditory processes has continued in collaboration with Prof. B.C.J. Moore (Cambridge) and with external funding from the Wellcome Trust and the EPSRC. It has provided new information that is additionally relevant to cochlear implant design. For example, we have shown that auditory processing of temporal information is "sluggish" (Carlyon, Moore, & Micheyl, 2000; Gockel, Carlyon, & Micheyl, 1999; Gockel, Moore, & Carlyon, 2001; Micheyl & Carlyon, 1998), suggesting that that the usefulness of pitch ("fundamental frequency, F0") information by cochlear implant users may be severely limited when F0 changes over time. This limitation would occur because modern implants code F0 in purely temporal terms. For example, we have shown that when the pitch of a sound is encoded only by temporal cues, one's estimate of that pitch is severely disrupted by subsequent and preceding sounds, even when they have a quite different F0 (Gockel et al., 1999; Micheyl & Carlyon, 1998). We have also developed a model of how listeners perceive the pitch of a sound whose frequency is changing rapidly over time (Gockel et al., 2001). In addition, a collaboration with Prof. S. Shamma (Univ. Maryland) has led to a new model of normal listeners' sensitivity to timing differences between frequency regions (Carlyon & Shamma, 2002), which has implications for across-channel timing sensitivity of cochlear implant users.

Another strand of our research concerns the independence of processing of location from other aspects of auditory perception (cf. proposal section SL2). In one study, we presented listeners with filtered pulse trains similar to those described above (A3.5), except that they were presented dichotically (Carlyon, Demany, and Deeks, 2001c). The perceived location of such dichotic pulse trains, presented over headphones, can be manipulated by varying the interaural time difference (ITD) between the pulses applied to each ear. In one crucial condition, we presented subjects with a pulse train that started off leading on the left ear, and was therefore heard on the left with a pitch equal to the pulse rate (200 Hz). Halfway through the sound, we switched the ITD of every other pulse pair, so that they led on the right (dashed lines in Fig. A3.3). Accordingly, subjects heard a new pulse train near the right ear. Importantly, though, the pitch they heard did not drop by an octave, as would be expected if they had segregated every other pair of dichotic pulses, assigned them to a new location, and then estimated the pitch of this segregated pulse train. Instead, the pitch remained unchanged (at 200 Hz), indicating that pitch was estimated from the rate of pulses arriving at each ear, whereas location was derived from the interaural timing relationship of the pulses. Another study showed that the detection of mistuning was also affected by "ear of entry", and not by the perceived location of the mistuned component relative to the rest of a complex tone (Gockel & Carlyon, 1998).

Fig. 3: Pulse trains used by Carlyon et al. (2001b). The repetition rate of the sound in the new location (dashed lines) is ½ that of the original sound, but its pitch did not drop substantially

Two further findings are worthy of particular mention. First, we have shown that stimuli with identical long-term power spectra, but which produce temporal patterns of stimulation of the basilar membrane that differ markedly in their peak factor ("peakiness"), can produce markedly different amounts of average excitation (Carlyon & Datta, 1997). This finding, obtained with forward masking and loudness-balancing procedures, reflects the fact that the peakier basilar membrane response is subjected to a greater degree of peripheral compression. It provides convincing evidence that peripheral compression acts on a fast time scale (faster than the 10-ms period of the fluctuations). Second, together with Prof. D. Bishop, we have provided evidence that specific language impairment in children is unlikely to be dependent on the child having a basic temporal processing deficit (Bishop, Carlyon, Deeks, & Bishop, 1999). This research, which won a "best paper" award from the journal in which it was published, has not been pursued since Prof. Bishop's move to the University of Oxford.

Project A4: Attention, consciousness and the body.

Consciousness and attention have long been intimately linked. This project explores that link by conceptual and empirical study of aspects of each that are often ignored. Generally, cognitive treatment of consciousness focusses on what is nonconscious rather than conscious, on formal features more than content, on external perception rather than experience of emotion, action or other aspects of the body or self; it largely ignores features that are so pervasive they escape notice, and it makes major ungrounded assumptions. In this period these neglected topics have continued to be pursued or are newly addressed, and the role of the body and space in consciousness has been emphasised.

Recent work challenges usual assumptions about unity of consciousness: (a) there is a single level of consciousness: if one has a phenomenal experience then one is aware of it and can report it; (b) there is (except perhaps in split-brain) only one consciousness per person: one cannot at one time experience both something and its contradiction; (c) the contents of one consciousness are integrated temporally and spatially, and if not we would notice. Studies of emotion experience, anosognosia for plegia, blindsight and unawareness of blindness (Lambie & Marcel, 2002; Marcel, 1998; Marcel et al., in press) have suggested two disunities: (i) Two levels of consciousness, 1st-order, phenomenal experience (qualitative representation, "what it's like") distinct from 2nd-order awareness of such experience, the latter being a function of attention and the basis of report and explicit episodic memory. (A pain in a body part attracts attention in virtue of its hedonic quality, but the attention creates awareness of it. In driving a known route while listening to the radio, the phenomenology of the driving exists but without 2nd-order awareness until attention is required). (See A4.4, A4.5). (ii) Disunity within each level: 1st-order experience is only locally unified and can be inconsistent; 2nd-order awareness can be dissociatively split into co-synchronous consciousnesses (Gallagher & Marcel, 1999; Marcel, 2000; Marcel, in press - a, b) (see A4.1). Two disregarded aspects of attention have been invoked as influencing the content and nature of consciousness: (i) attentional "mode", whether attention is detached or immersed, analytic or synthetic, and (ii) self- vs world-focus. Differences in the mode of attention have been used to account for abnormal states in anosognosia for plegia (Marcel et al., in press), for the sense of ownership/disownership of actions, bodyparts and tactile sensation (Marcel, in press - b), variations in emotion experience and hedonics, and the so-called "hard problem" – phenomenology itself (Lambie & Marcel, 2002). Self-/world-focus determines what one is focally aware of in emotion, in tactile experience, and in more general spatial experience.

Bodily experience plays an important role in gaining a sense of self, in emotion and in spatiality (Bermúdez, Marcel & Eilan, 1995; Lambie & Marcel, 2002; Marcel, in press - b). Work in this project and in A2 focusses on bodily spatiality, movement, awareness of them, and their role in emotion. First, conscious experience of bodily disposition has been shown to be qualitatively different from its corresponding nonconscious representation, both in use of kinesthetic imagery in recognition of bodyparts and in coding of disposition and location of limbs in control and awareness of action. Second, the content of perceptual consciousness depends on attention to the world or the body, one being spatial ground to the other as figure; and focal attention can be directed to parts of body space as to parts of external space. These foci of attention involve different spatial frames of reference, e.g. somatotopic vs egocentric (Marcel, submitted; Marcel & Dobel, in press). Thus, in touch attention determines whether the afferent information is experienced as tactile sensation at a somatic location or haptic perception of an object in egocentric space. This distinction is supported by our research on divided attention to points in somatotopic and external space. Several frames of reference are computed in perception and normally have to be integrated, e.g. in visually guided manipulation. However, in consciousness only one can be dominant at a time (Marcel, submitted; Marcel & Dobel, in press). Aspects of this are also explored in the work on somatic attention and neglect (Project A2.5).

A4.1 Anosognosia for plegia: Disunity of bodily unawareness

Scientific direction: Marcel (15%)

Other MRC posts: Postma (20%)

In anosognosia for plegia patients are unaware of their motor impairment. This topic is important for clinical practice as well as theoretically, since presence of unawareness of a deficit is the greatest impediment to rehabilitation. Joint research with Tegnér (Marcel et al., in press) that was large-scale in terms of number of patients and novel in terms of the breadth and depth of testing shows that unawareness for hemiplegia separates into several kinds of deficit, some patients manifesting more than one. (i) Patients aware of having plegia are unaware of its consequences. (ii) Patients who are unable to move a limb when asked are unaware of the failure, without illusory sensation of movement. (iii) Patients are concurrently aware of movement failures and can access episodic memory of these but are unable to update generic long-term body knowledge. (iv) Patients' awareness/unawareness of their limb paralysis or ability on bimanual tasks depends on manner of questioning ("Is this arm weak/Is this arm ever naughty?"; "In your present condition…/ If I were in your present condition…"), and they have a deficit of pragmatics and unconstrained confabulation specific to the affected limb(s). This is particular to right hemisphere damage, and it demonstrates disunified and split consciousness. A major thrust of this research is that its results undermine previous attempts to explain anosognosia for plegia in terms of a unitary deficit and indicate that it is not a matter of simple unawareness. The different forms of deficit have differential implications for rehabilitation. We are currently testing these characterisations (a) by assessing predicted differences in interference in colour-naming from plegia-related words at varying times after failed movement, (b) by comparing self-ratings with and without cued episodic recall of earlier movement failure, (c) by exploring what underlies split awareness and altered pragmatics by varying factors in the questions that elicit such dissociations and by exposing patients to their logical self-contradictions (see Proposals A4.1). We intend to develop our battery of tests into a clinical research tool.

A4.2 Conscious and nonconscious limb location and movement

Scientific direction: Marcel (15%)

A different aspect of bodily awareness is awareness of location and movement of limbs in normal people. In collaboration with Roll in Marseille, we have used vibrotactile-induced illusions of bodypart location. Vibrotactile stimulation of muscle spindle receptors at a joint produces illusory felt movement and corresponding illusory location of the limb if the limb is held stationary. With vision occluded, reports of and manual pointing to the felt location of the hand of the stimulated arm confirm the illusory displacement; yet if subjects are asked to grasp the seemingly displaced hand with their other hand, they do so correctly, in its true location. If the grasp is delayed it tends to go to the illusory location. This suggests that it is a proprioceptive version of the Roelofs effect (Bridgeman, 1992), where initial eye movements and pointing are accurate and dissociated from illusory visual target movement, but follow the illusion after a delay. In a second study, when the illusorily displaced hand has to move to a visually specified target location, with the arm unseen, the movement is almost always correct in both direction and extent. However, not only the prior intention but also (for c. 70% of people) the consciously felt movement is in the opposite direction to its actual direction, ie. that appropriate to the illusion. These disparities between reported experience and action imply (i) a dissociation of conscious experience of static bodily disposition from nonconscious representation of it, and of conscious intention from nonconscious implementation and control of movement, and (ii) that most people have poor conscious access to the specific implementation of intentions for movement. The first report of this work (Marcel, in press - b) also deals with experienced dis/ownership of action and the sense of agency. It provides a novel review and integration of a variety of neurological, neuroscience, normal cognitive and clinical research. In providing an account of ownership of action, especially regarding anarchic hand syndrome, it draws on the concept of detached versus immersed attention that has been applied in our work on anosognosia, emotion experience, and self awareness (see Gallagher and Marcel, 1999, for review).

A4.3 Effects of peripheral loss of sense of touch and body position

Scientific direction: Marcel (5%)

Other MRC posts: Gillmeister (10%)

Ongoing work with Cole (Southampton) on a patient who suffered peripheral deafferentation bears on conscious versus nonconscious bodily representation, on bodily experience and on spatial representation. Although most current neuropsychological research on these issues focuses on effects of central damage, the patient concerned confirms the importance of peripheral information and illuminates its roles. Due to a peripheral neuropathy that caused demyelinisation of the large afferent fibres, IW was deprived of all proprioceptive experience and bodily sensation beneath the neck, except for deep pain and temperature at the surface (Cole, 1993). (1) In experiments involving forced-choice discrimination of touch/no touch on a specified location, of location of touch, of presence-absence and direction of passive limb movement, and of joint position, IW performed above chance, suggesting some residual nonconscious capacities subserved by the intact slow fibres. (2) In order to assess determinateness of location of sensation, since IW cannot point to his own body we have used heat stimuli and required pointing to life-size depictions of a body and same-different judgements. IW has performed remarkably well. (3) Without vision IW's actions preserve configuration but not location. We have attempted to assess the extent to which his proprioceptive loss shows the same dissociation. We compared his ability to perceive and learn configurations versus egocentric locations of raised contours of shapes and of heat spots on a surface by manual exploration without vision. Although he was unable to do the first task, he did show the dissociation in the latter (though there are memory limitations). Since apprehension of configuration in this situation relies on proprioception, this suggests that the deficiency is not in proprioception per se, but in the representation of egocentric location. This also suggests that the deficiency is to some extent restricted to proprioceptive awareness. These studies thus reveal unexpected roles of peripheral afference. Further experiments will (a) refine our procedures since conventional paradigms are unpredictably difficult for IW, and (b) examine IW's ability to distinguish self-movement from world movement via a tactile flow-field of textured surfaces.

A4.4 Consciousness and emotion experience

Scientific direction: Marcel (15%)

Most current approaches to consciousness ignore emotion and bodily experience, dealing only with cognitive perceptual awareness of the external world. Our theoretical research on consciousness has been expanded with Lambie (Cambridge) to deal with emotion experience. Considerable conceptual and review work has resulted in a recent major theoretical paper (Lambie and Marcel, 2002), that has had an impact on cognitive and emotion theory and among philosophers. We have managed to resolve previous disputes as to the content of emotion experience by acknowledging its varieties and by treating separately the content of emotion experience, the underlying nonconscious correspondences, and the processes contributing to conscious experience. The proposed principled taxonomy of the content of emotion experience depends on three aspects of attention, mode (immersed-detached; synthetic-analytic), direction (self-world) and focus (evaluation-action), and is informed by a two-level view of consciousness where phenomenology (1st-order) is distinguished from awareness (2nd-order). Representation at the nonconscious and the two conscious levels can be distinguished respectively by indirect effects, expressability and ability to report. Intentional action based on a representation requires it to have phenomenological status, but without awareness of it appropriate explanation of one's action is impossible. These distinctions enable us to separate and account for cases of "unconscious" emotion where there is an apparent lack of phenomenology or awareness. Previously there has been no principled way to distinguish lack of awareness of one's emotion in normal cases, infancy, anger disorders, prefrontal brain damage, alexithymia, panic attacks, cultural differences, and defence mechanisms such as repression and intellectualization. Particular conceptual contributions of the work include (a) the mode of attention (a dimension of attention previously largely ignored), which accounts for phenomenology and hedonicity and is applicable to certain frontal right hemisphere neurological syndromes, (b) the role of the body in self experience and in a physical approach to emotion, (c) an integration of emotion experience with cognitive psychology, cognitive neuropsychology and the phenomenological tradition. The particular contributions to consciousness are in treating consciousness as two-level, separating phenomenology from awareness, in proposing how different aspects of attention contribute to each, and in outlining a spatial distinction between (bodily) self- and world-focus. The role of attentional mode in modulating felt ownership and hedonicity promises an approach to the "hard problem", i.e. phenomenology. Predictions from the theory will continue to be tested in the next quinquennium (see Proposals A4.4).

A4.5 Blindsight and visual awareness

Scientific direction: Marcel (5%)

Work on blindsight (Marcel, 1998) has shown several things. (i) In attempts to grasp objects in the blind field, aspects of patients' preparatory hand and arm movements are differentially appropriate to the relevant features of the object (shape, size, orientation, 3D location). This implies that nonconscious spatial representation is relatively intact, rather than being restricted to egocentric location. (ii) The fact that upper-case presentation of words in the blind field primes and biases choice of words subsequently presented in the sighted field implies that structural descriptions of features (oriented strokes) are achieved and that they can access appropriate stored representations, e.g. lexical entries. The original finding has been replicated and extended to representation of and priming by pictures by Joergens, Niedeggen & Stoerig (2001). (iii) Importantly, veridical phenomenal consciousness of static stimuli in the blind field can be temporarily regained if stimuli presented to it are related by Gestalt organisation to stimuli in the sighted field (using afterimages and Kanisza figures). This not only implies that blindsight does not involve a complete loss of conscious vision, but also suggests that the loss may be due to a reduction in attentional capacity. The relation of this effect to that of contralateral stimuli in extinction suggests that bilateral interaction across occipital cortices is integrative and facilitatory while that across parietal cortices is competitive (cf. distinct roles of cooperation and competition in visual attention; Project A1). We are testing this in currently planned joint research with Kentridge and Girolamo (see Proposals A4.2).

Research on an interesting single case suggests that blindsight is a 1st-order deficit of visual phenomenology (what characterises a perceptual experience as visual rather than of another sensory modality) rather than a 2nd-order deficit of perceptual awareness of or access to such phenomenology. DC's damage resulted from traumatic bilateral impacting of the occipital poles. DC was not clinically confused and was fully aware of his slight memory impairment and his broken legs. While he acknowledged from failures in behaviour that he had visual problems, he was not aware of being blind. Intentional denial to preserve self-esteem does not account for his selective unawareness. His adequate visual imagery performance (tested by Dr B. Wilson) suggests no problem with internally generated visual experience. His impairment thus appears to be a selective failure of introspective access to lack of visual perceptual experience. The most important aspect of the case is that while being blind on conventional testing, he has blindsight when tested appropriately. He could accurately point at and grasp objects when forced to do so rapidly. While performing at chance on conventional confident binary judgements of extremes of luminance, he performed nearly perfectly in the same situation when asked to rapidly guess luminance after it was explained that difficult discriminations would be used to measure thresholds. His unawareness of his "blindness" remitted after 7 months, but he has been left with bilateral blindsight. As indicated above, this double unawareness implies two levels of consciousness. Unfortunately the depression that his condition now causes him leads to reluctance to participate in further research.

Project A5: Integration and differentiation of frontal functions.

In Project A5 we turn to control functions, and in particular the functions of prefrontal cortex. While the importance of the prefrontal cortex for higher-order cognitive functions is largely undisputed, no consensus has been reached regarding the fractionation of functions within this region. In fact, most attempts to map specific cognitive functions onto neuroanatomical and/or cytoarchitectonic sub-divisions have been disappointing. This is true, not only for data derived from human neuropsychological studies, but also from lesion and electrophysiological studies in the monkey and, more recently, from human functional neuroimaging. Although functional specialization undoubtedly exists within the frontal cortex, it is becoming clear that the structural organization of this system does not relate, in any straightforward way, to contemporary models of cognition. Much of our research during the current funding period can be considered within this general conceptual framework and has involved, at multiple levels of analysis, attempts to identify adequate functional descriptions for specific regions within the human frontal lobe. Broadly speaking, three anatomically and cytoarchitectonically distinct frontal-lobe regions have been targeted, partly on the basis of previous work by Owen (mid-dorsolateral frontal cortex or DLPFC, comprising Brodmann areas 9 and 46; mid-ventrolateral frontal cortex or VLPFC comprising posterior areas 47 and 45) and Rogers (orbitofrontal cortex comprising Brodmann area 11), and partly on the basis of other monkey and human data suggesting some specialization of these areas in respectively executive, mnemonic and affective processes.

A5.1 The functional relationship between DLPFC and VLPFC

Scientific direction: Owen (25%)

Other MRC posts: Duncan (5%)

Grant-supported posts and visitors: Bor

Students: Bor, Lee

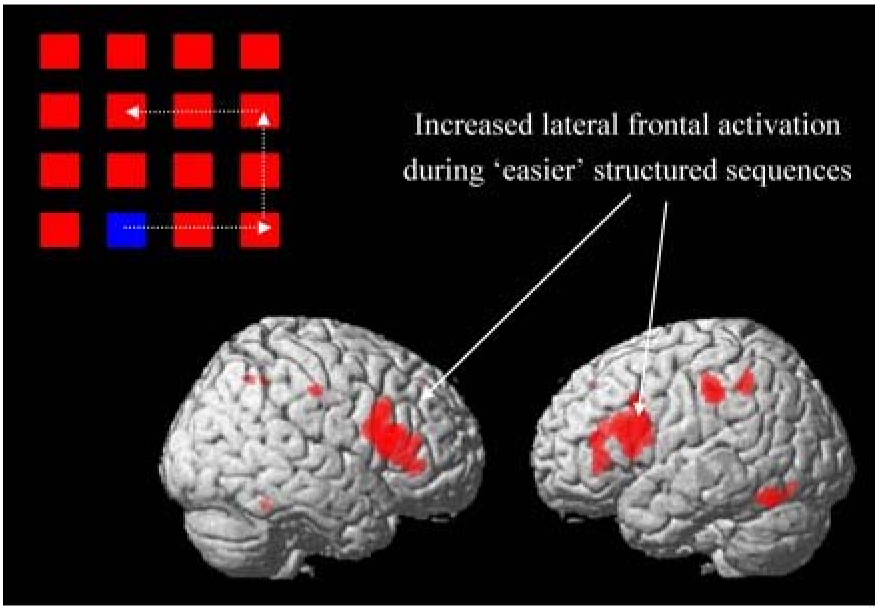
Perhaps the most widely debated issue to have emerged in this field in recent years concerns the functional relationship between dorsal and ventral regions of the lateral frontal cortex. One prevalent view has been that these regions differ in terms of the type (e.g. domain) of information being processed (Goldman-Rakic, 1994), with dorsolateral frontal regions being principally concerned with spatial material while ventrolateral regions preferentially process non-spatial material. Owen has combined studies in neuropsychological patients (Owen, Morris, Sahakian, Polkey, & Robbins, 1996c), with functional neuroimaging studies in healthy volunteers (e.g. Owen et al., 1997a; Owen et al., 1998b; Owen et al., 1999b; Owen, Lee, & Williams, 2000) and extensive reviews of both the functional neuroimaging (Owen 1997a; 1997b; 2000) and electrophysiological work (Rushworth & Owen, 1998) literature to refute this view in favour of a "process-specific" model of lateral frontal-lobe organisation (Petrides, 1994). According to that view, the DLPFC and VLPFC differ, not in terms of the modality of the information that is processed by these regions, but in terms of the type of processing that is carried out on that information. For example, while VLPFC but not DLPFC is activated during simple spatial (Owen et al., 1999b), digit (Owen et al., 2000) and pattern span (Stern et al., 2000) tasks, activation in both regions is observed when participants are required to manipulate that same information within memory (e.g. Owen et al., 1998b; 1999b; 2000).

Though these studies render the material-specific model untenable, they provide only preliminary hints as to what the functional contribution of DLPFC and VLPFC might actually be. For example, terms such as "manipulation" (Owen 2000) and "monitoring" (Petrides, 1994) which have been used to describe DLPFC function can be hard to define operationally, and in many studies, a complicating factor has been simple task difficulty; tasks that produce greater DLPFC activation (e.g. reverse digit span, Owen et al., 2000) tend to be more difficult than those that do not (e.g. forward digit span). This confound is important because increasing task difficulty in itself is associated with DLPFC activation in many different cognitive domains (Duncan & Owen, 2000, see A5.7).

Two PET studies in healthy controls (Bor, Duncan, & Owen, 2001) provided an interesting new approach to this problem; the results revealed that while traditional spatial span tasks (with randomly arranged unstructured arrays) typically activate the VLPFC, analogous tasks using a more structured spatial array activate both VLPFC and DLPFC. Moreover, performance on the more structured task was rather better than performance on the unstructured task suggesting a lowering of overall task demands. These studies were complemented and extended by a large-scale public science exhibit at the Science Museum in London (Bor, Duncan, & Owen., in press) involving several thousand participants. Verbal protocols suggest that, with structured arrays, there is increased reliance on array-specific encoding strategies which serve to reduce the overall load on working memory.

To test this hypothesis directly, a novel version of the spatial span task was developed to compare structured span sequences, encouraging reorganization and chunking, with unstructured sequences, using event-related fMRI (Bor et al., in press). As predicted, structured sequences led to improved performance yet, despite this reduction in task difficulty, the DLPFC and selected regions of posterior cortex were more strongly recruited (see Figure A5.1). Additional behavioral evidence from the scanned volunteers as well as thousands of participants involved in the Science Museum project suggested that this was the result of reorganizing the material to be remembered into familiar chunks. For the first time, we believe, these results show that even when memory demand decreases, organization of working memory contents into higher-level chunks is associated with increased DLPFC activity.

A5.1 Structured sequences are easier to remember than non-structured sequences yet produce significantly great activity in the lateral frontal cortex.



Convergence between functional neuroimaging and lesion studies remains a central theme in this work and the imaging results make a number of important predictions about the behaviour of frontal-lobe patients. In particular, they suggest impairments in simple working memory tasks such as spatial span, perhaps with disproportionate deficits in tasks that depend upon strategies to optimize performance. While previous work by Owen (Owen et al., 1996c) has suggested that frontal-lobe patients are particularly impaired at working memory tasks involving strategies, the existing literature on the classic spatial span task of Corsi suggests that memory tasks of this type are not impaired in such patients (e.g. Owen, Downes, Sahakian, Polkey, & Robbins, 1990). To explore the relationship between neuropsychological studies and imaging studies in healthy volunteers further, a more sensitive method for measuring spatial span was developed (Bor et al., submitted) and used to test patients from the Cambridge Cognitive Neuroscience Research Panel. Consistent with the imaging data, the preliminary results show that patients with frontal-lobe damage are indeed impaired at the more sensitive spatial span tasks, and may be disproportionately impaired when chunking strategies are available.

A5.2 The VLPFC: Unitary or multiple functions

Scientific direction: Owen (25%)

Other MRC posts: Dove (3 years, 80%)

Students: Bor

A parallel series of studies has investigated VLPFC function in detail. Earlier work by Owen using PET had suggested that reliable activation is observed in this region during tasks that require "active" retrieval of spatial information from working memory (Owen et al., 1996a; 1998b; see also Bor et al., 2001; in press). Follow-up studies confirmed that this involvement in retrieval was polymodal; identical patterns of activity were observed in this region during analogous tasks involving auditorily presented digits (Owen et al., 2000), and visually presented abstract patterns (Stern et al., 2000; Owen et al., 1998b).

On the basis of these findings, Dove and Owen have used event-related fMRI to define the specific role of this region in mnemonic processing. The results of the first study, using abstract patterns, demonstrated that VLPFC is similarly involved in encoding and retrieval while preliminary results from a follow-up investigation suggest similar results for face and location stimuli. In both studies, however, the critical requirement for VLPFC activity appears to be intention. That is, while passive (unintentional) encoding and retrieval produced reliable activity in the hippocampal formation bilaterally (Dove, Brett, Cusack, & Owen, submitted), even in individual participants, robust activation was only observed in VLPFC when participants were explicitly instructed either to encode or to retrieve.

Parallel studies suggest, however, that VLPFC functions extend beyond the domain of memory. For example, in one collaborative event-related fMRI study with Professor T. W. Robbins and colleagues in the Department of Experimental Psychology, Cambridge (Cools, Clark, Owen, & Robbins, 2002b), highly significant activity was observed in this region during a probabilistic reversal learning task which places minimal demands on memory; specifically during a critical last reversal error, at which point subjects stopped responding to a previously relevant pattern and reversed responding to a newly relevant pattern. Results such as these, in combination with the series of memory studies described above, illustrate the difficulty associated with developing a theory of frontal specialization which is sufficiently comprehensive to incorporate the main findings from ostensibly different types of cognitive task. On the basis of evidence accumulated thus far, it has been hypothesized that a general role for VLPFC is to map and implement arbitrary learned responses to specific stimuli for guiding behaviour (Owen, 2000).

A5.3 The role of the orbitofrontal cortex

Scientific direction: Owen (10%)

Other MRC posts: Rogers (6 months, 20%)

Grant-supported posts and visitors: Hinton, Arana

Data from human neuropsychology suggest that the functions of orbitofrontal cortex are quite distinct from those of lateral frontal regions, involving aspects of emotional and social decision making. For example, patients with damage to the orbitofrontal cortex exhibit marked impairments in laboratory based gambling or risk-taking tasks, suggesting that this part of the human frontal cortex contributes to complex decision making. In one series of PET studies the functions of the DLPFC and orbitofrontal cortices were compared explicitly, while in later studies the role of the orbitofrontal cortex in complex decision making was investigated. PET was used in both cases since the most ventral parts of the frontal lobe remain susceptible to acquisition artifacts when imaged using fMRI. In an initial study, a novel gambling task developed by Rogers (Rogers et al., 1999) was used. The task involved predicting which of two mutually exclusive outcomes would occur, but critically, the larger reward (and penalty) was associated with choice of the least likely outcome whereas the smallest reward (and penalty) was associated with choice of the most likely outcome. Resolving these "conflicting" decisions was associated with three distinct activation foci within the inferior and orbitofrontal prefrontal cortices. By contrast, increases in the degree of conflict inherent in these decisions was associated with only limited changes in the orbitofrontal cortex. These results suggest that decision making recruits multiple regions of the human inferior frontal cortex, receiving information from a diverse set of cortical and limbic inputs, and that the contribution of orbitofrontal regions may involve processing changes in reward-related information (Rogers, 1999). By adapting this same task to include a working memory component, this project has been extended through a further PET investigation and, more recently, an event-related fMRI study, to test whether the DLPFC and orbitofrontal cortices can be shown to be disproportionately involved in mnemonic processing and decision making, respectively (Rogers et al., in preparation). While the results partially confirm this hypothesis, they also demonstrate that such functional distinctions, even between anatomically and cytoarchitectonically distinct frontal regions, are far from absolute.

In a related series of investigations using PET, the relationship between the orbitofrontal cortex and the limbic system in aspects of motivation and reward has been investigated using primary reward (food) as an experimental variable. Motivation impacts on all forms of cognition and behaviour and can mediate both the vigour and direction of responses. The orbitofrontal cortex, which has direct neuronal connections with various limbic structures, including the amygdala, is well placed to code information about the motivational or reward value of incoming information. Psychologically, one can distinguish between motivational mechanisms that subserve homeostatic regulation (sometimes referred to as drive) from processes that identify highly attractive goals in the outside world (a process of incentive learning) which subsequently guide our actions. With respect to food motivation, previous imaging studies have identified hunger-related brain activity in imaging studies, but none, as yet, have specifically studied incentive processes. In one collaborative PET study with Drs A. Roberts, J. Parkinson and colleagues of the Department of Anatomy, Cambridge and Professor T. Holland and colleagues of the Department of Psychiatry, Cambridge, the effect of varying the incentive value of food stimuli was investigated in healthy volunteers along with the effect of having to make an affective decision relating to these stimuli. This was achieved through the presentation of restaurant menus which were tailored to individuals' food preferences and varied along two dimensions; incentive (high incentive or 'liked' foods versus low incentive or 'no particular preference' foods) and decision making (decision 'which would you prefer to eat' versus no decision 'consider each of these menu possibilities'). As predicted, varying the incentive value of the food stimuli activated the amygdala, but importantly, had no effect on the orbitofrontal cortex. In contrast, decision making activated the orbitofrontal prefrontal cortex, and in particular, affectively laden decisions (interaction between incentive value and decision making) produced significantly increased activity in this area.

A5.4 Lateralization of function within the prefrontal cortex

Scientific direction: Owen (10%)

Students: Lee

The issue of lateralization of function within the frontal lobe has also received considerable and renewed attention in recent years, fuelled primarily by a plethora of functional neuroimaging studies. While several of these studies have suggested that specific cognitive processes such as episodic memory encoding and retrieval may be strongly lateralized within the frontal lobe, an extensive review of the relevant imaging literature failed to provide convincing support for this functional asymmetry model (Lee, Robbins, & Owen, in press-a). Instead, we have suggested (Lee et al., 2000; Owen, Milner, Petrides, & Evans, 1996d) that episodic memory encoding and retrieval may actually involve similar regions of the lateral prefrontal cortex when all factors relating to the type of stimulus material (e.g. modality) are appropriately controlled, a position that concurs fully with results emerging from the parallel studies of working memory described above (e.g. Dove et al., submitted). To test this hypothesis directly a series of PET and fMRI studies has been conducted in collaboration with Professor T. W. Robbins and colleagues in the Department of Experimental Psychology, Cambridge and Professor P. Mathews and colleagues at the MRC Centre for Functional Magnetic Resonance Imaging of the Brain (FMRIB), Oxford. In one PET study (Lee, Robbins, Pickard, & Owen, 2000), easily verbalisable material lead to activation predominantly in the left lateral frontal cortex whilst non-easily verbalisable material lead to activation predominantly in the right lateral frontal cortex, in both cases irrespective of encoding and retrieval processes. In order to replicate and extend these findings, the same task was modified for use with fMRI (Lee et al., in press-b). It was found that, in comparison to a baseline condition, the encoding of visual stimuli led to a bilateral activation of the prefrontal cortex whilst the encoding of verbal stimuli led to a preferential activation of the left prefrontal cortex. An effect of stimulus type was less evident during retrieval with both visual and verbal stimuli leading to bilateral prefrontal cortex activation. Overall, encoding and retrieval activated similar regions of the prefrontal cortex. To extend these findings further, the tasks used in the fMRI study were used to assess a group of patients with unilateral frontal lesions and a group of healthy controls. The patients were significantly impaired compared to the healthy volunteers, although no significant differences were found in performance between the right- and left-sided lesioned patients. This result suggests that memory-related asymmetries sometimes observed during functional neuroimaging studies may not be critical for task performance.

A5.5 Frontostriatal interactions

Scientific direction: Owen (10%)

Other MRC posts: Dove (20%)

Our studies in patients with Parkinson's disease (PD) have revealed a progressive pattern of neuropsychological impairment, which, in its earliest stages, resembles that seen after damage to the frontal lobes (e.g. Cools, Stefanova, Barker, Robbins, & Owen, 2002a, Cox; Stefanova, Johnsrude, Robbins, & Owen, 2002; Dagher, Owen, & Brooks; 1999; Dagher, Owen, Boecker, & Brooks, 2001; Hodgson, Tiesman, Owen, & Kennard, 2002; Owen, 1997c; Owen, Iddon, Hodges, & Robbins; 1997; Owen, Doyon, Dagher, & Evans, 1998a; Owen, Doyon, Dagher, & Evans, 1999a; Owen, Sahakian, & Robbins, 1998c; Owen & Doyon, 1999). However, since PD is associated with both striatal and prefrontal dopamine loss, it is unclear whether these 'frontal-like' cognitive deficits result from one, or both, of these forms of pathology. This issue has implications both for the clinical management of PD patients and for our understanding of the functional relationship between frontal cortex and basal ganglia. In one study, PET was used to examine how regional blood flow in the frontal cortex and in the basal ganglia may be affected in patients with PD, during tests of planning and working memory (Owen et al., 1998a; 1999a; Cools et al., 2002a). Though patients showed no significant impairments in prefrontal cortex, differences were consistently observed in one subcortical area centred on the right internal segment of the globus pallidus (Gpi). This region constitutes the main basal ganglia outflow nucleus by which descending cortico-striatal inputs project back to discrete frontal regions. The results suggest that "frontal" cognitive deficits seen in early PD are in part the result of abnormal processing of prefrontal input through malfunctioning basal ganglia circuitry.

In a collaborative follow-up study with Drs R. Barker and S. Lewis of the MRC Centre for Brain Repair, Cambridge and Professor T. W. Robbins and colleagues from the Department of Experimental Psychology, Cambridge, fMRI was used to examine this issue further and to attempt to identify functional neuroanatomical 'markers' of executive dysfunction in PD patients. A sub-group of patients with executive deficits were shown to be impaired at manipulation, but not retrieval, within verbal working memory compared to a group of patients with no predefined executive impairments (Lewis et al., in press). Examined with fMRI, those patients with executive deficits showed reduced working memory activation in specific striatal, and this time also frontal-lobe, sites. No such changes occurred in patients who were not cognitively impaired. These results demonstrate, for the first time, that cognitive deficits in PD are accompanied by neural changes that are related to, but distinct from, those changes which underlie motoric deficits in these patients and that fMRI may provide a valuable tool for identifying those patients who may benefit maximally from targeted therapeutic strategies (Lewis, Dove, Robbins, Barker, & Owen, submitted).

A5.6 The frontal lobes: pharmacological mechanisms

Scientific direction: Owen (10%)

Local injection and iontophoretic application of specific dopaminergic agents as well as electrophysiological measures in the monkey suggests that the dorsolateral frontal cortex is the critical locus for dopaminergic effects on high-level cognitive functions, although little is known about these effects in humans. This issue has been investigated in collaborative imaging studies with Professor T. W. Robbins and colleagues in the Department of Experimental Psychology, Cambridge and Dr. B. J. Sahakian in the Department of Psychiatry, Cambridge (Mehta et al., 2000; Cools, Stefanova, Barker, Robbins, & Owen, 2002a), one using methylphenidate in healthy control volunteers and the other using L-dopa in patients with Parkinson's disease. In the first study, the changes in regional cerebral blood flow induced by methylphenidate during the performance of a spatial working memory task were investigated to define the neuroanatomical locus of the beneficial effect of the drug (Mehta et al., 2000). The results showed that the methylphenidate-induced improvements in working memory performance occur with task-related reductions in blood flow in the dorsolateral frontal cortex. This was, to our knowledge, the first demonstration of a localization of a drug-induced improvement in spatial working memory performance in humans. In a second study (Cools et al., 2002a), we used PET to examine the critical locus of the effect of dopaminergic medication on high-level cognitive functioning in Parkinson's disease by comparing their rCBF 'on' and 'off' L-dopa. L-dopa was shown to effectively normalize blood flow in the right dorsolateral prefrontal cortex during planning and spatial working memory and a significant correlation was found between L-dopa-induced, planning-related blood flow decreases in the right dorsolateral prefrontal cortex and L-dopa-induced changes in performance on the planning task. The results of these two investigations are consistent, yet surprising, in demonstrating that dopaminergic agents improve performance on tests of working memory (and planning) by reducing blood flow in the dorsolateral frontal cortex. On this basis we have hypothesized that the observed dopamine-related blood flow reductions reflect increased efficiency, in a manner described previously by Furey, Pietrini, & Haxby (2000) for acetylcholine.

A5.7 Spearman's

Scientific direction: Duncan (20%)

Other MRC posts: Parr (100%)

The broad disorganization of behaviour that can follow prefrontal lesions is reminiscent of a key concept from psychometrics - "general intelligence" or Spearman's g (Spearman, 1904). Conventional intelligence tests are important because of their broad prediction of success in many different cognitive domains. In the previous funding period, we proposed that tests of this sort in large part measure an aspect of prefrontal function. In the current period, this proposal has been followed up with functional neuroimaging, in patient studies and in studies of normal cognition.

Using PET (Duncan et al., 2000), we tested two classical hypotheses concerning conventional intelligence tests. One, following Spearman (1904), is that these tests measure some specific but generally important aspect of cognitive function. This predicts focal brain activation; we predicted in particular focal activity in prefrontal cortex. The alternative, following Thomson (1951) and many others, is that intelligence tests measure an "average" of the brain's major cognitive functions, predicting diffuse activation in systems related to language, spatial processing, memory, knowledge and so on. The results were clearly in line with the Spearman hypothesis, showing focal activation in both DLPFC and VLPFC, with additional less consistent foci in premotor and inferior parietal cortex.

Patient studies have made use of the Cambridge Cognitive Neuroscience Research Panel, now including >25 patients with focal frontal lesions mapped by MRI, and a similar number of posterior controls. Using the methods of Brett et al. (2001) (see Project MR2.3), lesions are traced in standard atlas coordinates, allowing direct cross-reference to functional imaging results. The results suggest that familiar neuropsychological tests (Wisconsin card-sorting, verbal fluency) differentiate frontal and posterior lesions only by virtue of their shared variance with a standard test of fluid intelligence. We are also beginning to understand variability of cognitive impairment among prefrontal patients; orbitofrontal lesions, in particular, produce little or no fluid intelligence impairment. As patient numbers increase, we plan to address finer distinctions within prefrontal cortex (see following section A5.8).

In studies of normal function, we seek a cognitive interpretation of g. A characteristic of some frontal patients is goal neglect, or disregard of some task requirement though it can be understood and recalled. As described in the previous funding period (Duncan, Emslie, Williams, Johnson, & Freer, 1996), goal neglect can also be seen in the normal population, where it is strongly related to Spearman's g. In our tasks, explicit prompting always causes this neglect to resolve. We have now repeatedly confirmed the close association of goal neglect and Spearman's g. This association is identical in normal participants, frontal-lobe and posterior patients. Goal neglect is insensitive to concurrent task demands, requirements for sustained attention, and recency of task switches. Indeed, preliminary data suggest that immediate, concurrent task demands can conceal the relationship between error and g. Instead, the important consideration may be the overall complexity of task rules.

Though this is ongoing work, our hypothesis is that specific regions of prefrontal cortex play a role in constructing an on-line model of current task events, including relevant inputs, outputs, facts and rules from semantic memory etc. The adequacy of this process is largely reflected in Spearman's g. In goal neglect, task components compete for representation; components can be lost from the active model though still available for explicit recall.

A5.8 The adaptive coding model

Scientific direction: Duncan (10%)

Other MRC posts: Owen (5%)

Very recently, we have proposed a new perspective on prefrontal function (Duncan, 2001; Duncan & Miller, 2002). In over 20 years of animal (Goldman-Rakic, 1988) and imaging (Cabeza & Nyberg, 2000) studies, a dominant theme has been that particular regions of prefrontal cortex should be strongly specialized for particular cognitive functions. In our adaptive coding model, the emphasis instead is on flexibility or plasticity of neural function.

In a systematic literature review (Duncan & Owen, 2000a, b), we synthesized data from all published studies dealing with 5 different types of cognitive demand - inhibition of prepotent responses, task novelty, working memory load, working memory delay, and perceptual difficulty. In one respect, activations within prefrontal cortex showed clear structure, with strong clustering of activations in and around the inferior frontal sulcus (including the DLPFC region described above), along the frontal operculum towards the anterior insula (the VLPFC region above), and in the dorsal anterior cingulate. For the remainder of prefrontal cortex - including most of the medial and all of the orbital surfaces - there was little or no evidence of demand-related activity. As regards cognitive domain, however, there was no evidence for regional specialization. Activation patterns associated with all five demands were closely similar (Figure A5.2).

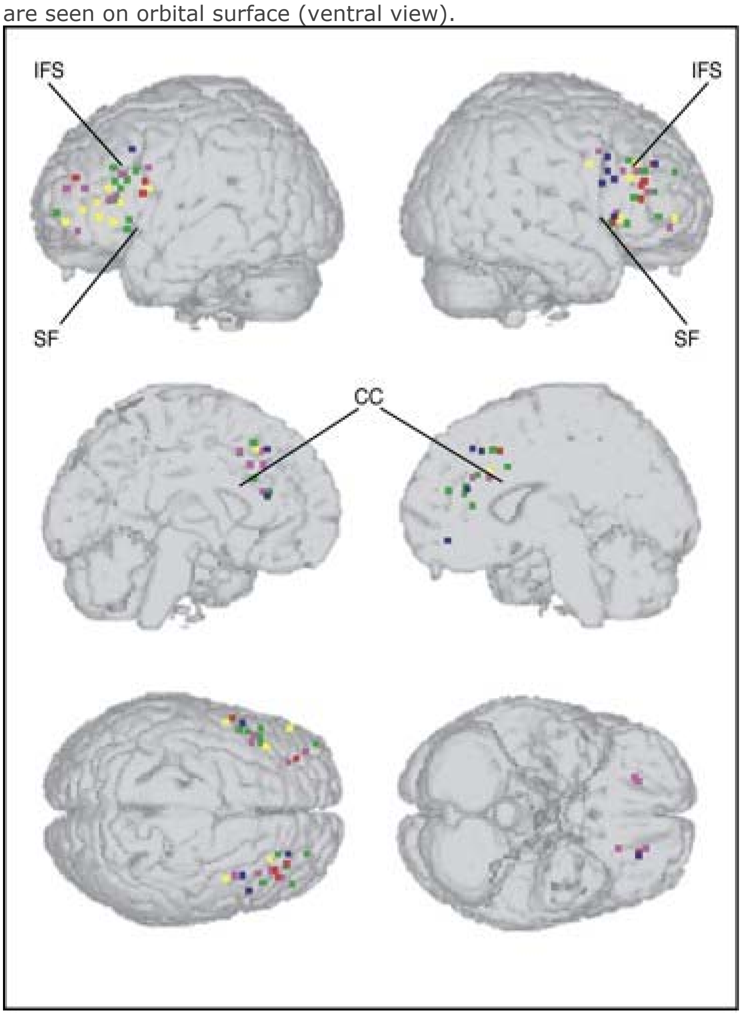
In the adaptive coding model (Duncan, 2001a; Duncan & Miller, 2002), we propose that individual frontal neurons must be highly plastic in the information they code. Neural properties adapt to the current task context, producing a dense, distributed representation of relevant task information and events. This model casts light on the roles of frontal cortex in working memory, attention and control. As regards working memory, prefrontal cortex produces a representation of just that information of relevance to a current task (see A5.7 above). As regards attention, prefrontal cortex filters out information of no current importance. As regards control, we propose that selective prefrontal representation of task-relevant information produced the "bias" signal (see Project A1) driving related coding in posterior and subcortical systems.

To some extent at least, flexibility is the converse of specialization. At least for much of the lateral surface, we suggest that regional specialization is statistical rather than absolute (Duncan, 2001a; Duncan & Miller, 2002), reflecting different but overlapping regional distributions of potentially relevant cells for different aspects of task representation. This proposal is consistent with the hints of regional specialization in our imaging studies, coupled with difficulty in establishing strong double dissociations. Direct tests are planned in the next funding period.

Project A6: Monitoring, arousal and sustained attention.

Investigations into the methodologically difficult area of executive, higher-level control processes have increased dramatically in the last decade or so - not least reflecting the importance of dysfunctions of this type in determining clinical outcome following brain injury. Aspects of a dysexecutive syndrome (a term coined by Baddeley and Wilson at the Unit in 1988) are common following traumatic brain injury (TBI - affecting approximately 35 per 100,000 of the population, predominantly young men), along with other causes of brain damage, and are increasingly being implicated in a number of developmental conditions including attention deficit hyperactivity disorder (ADHD).

Figure A5.2 Prefrontal activations from studies of response conflict (green), task novelty (purple), number of elements in working memory (yellow), working memory delay (red) and perceptual difficulty (blue). On the lateral surface, there are activation clusters around the inferior frontal sulcus (IFC) and frontal operculum/insula (here projected onto lateral surface, just anterior to Sylvian fissure SF). On the medial surface, activations are largely restricted to the dorsal anterior cingulate (above corpus callosum CC). Even for dorsolateral surface there are large areas without activations (dorsal brain view); only occasional activations are seen on orbital surface (ventral view).



Any factor that limits the goal-directed expression of other abilities in everyday life should be a high priority for rehabilitation. To date, relatively few systematic attempts to remediate dysexecutive disorders have been reported. As the very functions that may facilitate functional recovery in other capacities (error detection, flexible adaptation, development of compensatory strategies and so forth) are those that are compromised, this is an inherently challenging task. There are two principal aims within Project A6. The first is to make strong links between basic experimental/functional imaging and theoretical development in this area and the development and assessment of useful rehabilitative techniques. The second is to use results of rehabilitation studies to further constrain and develop theory. Dissemination of research findings to clinical colleagues, including scientific reviews of the theoretical and empirical basis of rehabilitation, has continued throughout this funding period (Manly, in press; Manly & Robertson, 1997; Manly & Robertson, in press; Manly et al., 2002b; Robertson, 1998b; Robertson, 1999a; Robertson, 1999b; Robertson, 1999c; Robertson, 1999d; Robertson, 2000; Robertson & Murre, 1999)

A6.1 Sustained attention / Goal monitoring

Scientific direction: Robertson (2 years, 20%), Manly (30%)

Other MRC posts: Cusack (5%), Evans (5%)

Grant-supported posts and visitors: Rorden, Datta

A key function in achieving goals is the capacity to keep a goal/plan actively in mind and to maintain a particular processing stance - even in the absence of strong or continuous environmental triggers for that state. The Sustained Attention to Response Test (SART: (Robertson, Manly, Andrade, Baddeley, & Yiend, 1997a) was designed to form a simple and tractable model of such situations. In the task, participants are asked to watch a succession of single digits appearing on a computer monitor at a regular pacing of approximately 1 digit per second. The aim is simply to press a single response key as each digit appears with the exception of a nominated no-go digit, to which no response should be made. As the no-go trial appears infrequently within the random sequence of digits, it was hypothesized that participants would tend to neglect this goal, and instead lapse into a rather absentminded repetitive response mode. Not only are errors common within the normal population, but the frequency of those errors is significantly related to individual propensity to absentminded slips in everyday life, as assessed using standardised self- and informant-report questionnaires (Manly, Robertson, Galloway, & Hawkins, 1999). This relationship between a controlled and reliable computer task and lapses in complex everyday situations is also present in the TBI population (Robertson et al., 1997a). Investigations on the predictive relationship of the SART to other neuropsychological and everyday functioning measures in the brain injured population are continuing with Evans and colleagues at the Oliver Zangwill Centre.

The SART lends itself to experimental manipulation. Recent work has demonstrated a) that the key demands of the task lie in the duration of the intervals between no-go target presentations (Manly et al., 1999); and b) that accounts of individual differences in performance couched purely in terms of speed-accuracy trade-off are not adequate (Manly, Davison, Heutink, Galloway, & Robertson, 2000b). Perhaps the most compelling demonstration that performance on the SART depends upon the maintenance of active top-down control (in addition to - or in order to exert - any response inhibition capacity) comes from the results of cueing studies. Across three studies, patients and healthy controls were exposed to occasional and randomly timed auditory tones as they performed the test. They were asked to use the tone as a cue to think about what they were doing. Although participants, if asked, have invariably been able to remember what they should be doing during the task, these spaced reminders nevertheless act to significantly improve performance. This suggests that exogenous cueing - or perhaps crucially, interruption to current activity - can allow participants to better maintain a link between a remembered goal and their subsequent actions (Manly et al., submitted-a).

A difficulty in study of brain injury is the possibility of damage to multiple systems separately affecting task performance. One alternative approach is to examine within-subject modulation of normal performance. Previous research suggests that activities performed late at night, early in the morning, or by sleep-deprived people are more vulnerable to absentminded slips and can be strikingly similar to the performance of dysexecutive patients. Neurophysiological studies further suggest that sleep onset and offset is not expressed as a uniform effect across the brain, but one that disproportionately de-activates particular regions, including frontal cortex. Repeated assessment of young healthy subjects over four days showed that the capacity to withhold responses in the SART - and by inference to actively maintain a simple goal in mind - indeed showed clear circadian variation. As might be predicted on the basis of automatic/controlled processing distinctions and their relationship to prefrontal function, the more routine, overlearned aspects of the task were wholly unaffected (Manly et al., 2001b).

Taking advantage of the tight temporal resolution of event related potentials (ERPs), we examined whether electrophysiological signals could be used to predict subsequent success or failure on a no-go trial, thereby forming a marker of attentional allocation. The results showed that the P300 component (often attributed to attentional processing) was reduced in trials that preceded an action slip (Datta et al., submitted; Manly et al., 2000a). Initial analysis of data collected in collaboration with colleagues at the Rotman Institute in Toronto further suggests that the P300 is relatively suppressed in TBI patients - who are prone to high error rates - as they perform the task (Armilio, Picton, Robertson, & Stuss, 1999).

Work comparing TBI patients with healthy controls suggests, perhaps counterintuitively, that a fixed sequence version of the SART (e.g., requiring a response to be withheld to the number 9 in the repeating sequence 1 2 3 4 5 6 7 8 9 1 2 3 …) is actually more sensitive to the patients' impairments than the more challenging conventional random sequence. We have therefore suggested that the low demands of this ostensibly trivial task - together with the long intervals between no-go trials - may exacerbate the patients' difficulty in maintaining a sufficiently alert and goal-focused state. Comparison of regional cerebral activation associated with the two conditions supports this view. In a PET study, performance of the fixed sequence SART (which attracts errors even in healthy volunteers) was associated with significantly increased blood flow above the random sequence in regions previously limited to sustained attention - specifically within right dorsolateral prefrontal and parietal areas (Manly et al., 2001c; Manly et al., submitted-b).

Some patients with a dysexecutive syndrome show a clear dissociation between stated intention and subsequent action. As demonstrated by Duncan and colleagues (Project A5) milder forms of such goal neglect can be observed within many of the brain injured and - to a lesser degree - in the normal population. Building on the experimental work described above, with Evans and colleagues at the Oliver Zangwill Centre, we sought to examine the effect of environmental cues/interruption of current activity on patients' performance in a task that seeks to replicate some of the complexities of everyday life (where the impact of dysexecutive deficits are most apparent). In a variant of Shallice and Burgess's (1991) Six Elements test, we asked head-injured patients to try to perform at least some of each of five different activities within a fifteen-minute period. As finishing each component task would take longer than the total time available, the test placed emphasis on patients' ability to keep in mind the main goal (to do at least some of each task) and to switch flexibly between tasks at suitable points. In line with previous findings, and despite clear comprehension and memory for the instructions, the performance of dysexecutive patients deviated sharply from that of IQ matched controls - the key error being to get caught up in one particular task to the detriment of the main goal. The use of a randomly timed tone to periodically interrupt ongoing performance not only significantly improved the patients' performance, but rendered it indistinguishable from that of the healthy control group (Manly et al., 2001a). Such results have value in assessment (for example, in ruling out the impact of poor memory as a cause for impaired performance) and suggest that appropriate environmental cueing could minimise the handicap associated with these deficits in everyday situations. The use of technologies (such as palm-top computers or vibrating watches) to perform this cueing function in everyday life is an area that we are actively exploring in collaboration with the Oliver Zangwill Centre.

Developments in the investigation of control functions have largely been conducted in Western countries and with English Speaking populations. With Chan, we examined the applicability of widely used clinical measures (Six Elements Task, Tower of Hanoi) and informant/self report checklists of dysexecutive behaviours (Broadbent's Cognitive Failures Questionnaire, the DEX dysexecutive questionnaire) within healthy and head-injured Cantonese speaking Hong Kong residents. The results suggest that the overall levels of performance and discrepancies between head injured and healthy participants, and the relationships between the tasks and checklist ratings, are robust across this cultural difference (Chan & Manly, 2002).

A6.2 Attention and higher level control in children

Scientific direction: Robertson (5%, 2 years), Manly (30%)

Students: Dobler

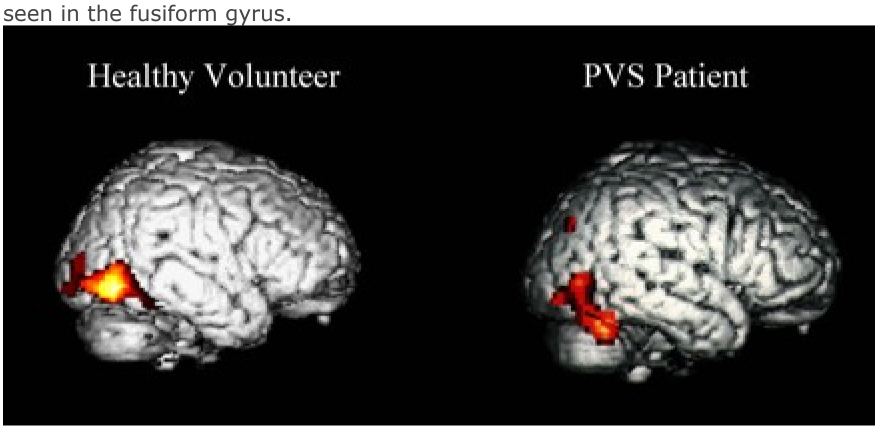
Vast and increasing numbers of children are referred to clinical services with suspected attentional problems. In some studies, referral rates for ADHD have reached 6% of all school age boys and 1.5% of girls. Deficits in attention processes have been implicated in many other developmental conditions including autism and Tourette's syndrome, and following acquired brain damage in childhood. Despite the scale of the perceived difficulty, there has been somewhat of a dichotomy between approaches in attention within the adult and developmental literature. While for adults, neuroscientific analysis of functional and neuroanatomical separations in attention systems has fed through into improved assessment and targeted rehabilitation, diagnosis of childrens' attention deficits continues to rest almost exclusively on parental and teacher reports. As discussed in Project A2, the observation of unilateral neglect-like phenomena in children led us to adapt and collect normative data on a range of targeted performance-based attention measures. Among the measures now incorporated into the Test of Everyday Attention for Children (Manly et al., 2002a) were variants of the SART and the simple tone counting measure of sustained attention first developed by Wilkins and colleagues at the Unit. To date, we have applied this differential assessment approach to children diagnosed with ADHD and acquired brain injury (Anderson, Fenwick, Manly, & Robertson, 1998; Micallef, Anderson, Anderson, Robertson, & Manly, 2001). Disproportionate deficits in maintaining a simple goal/sustained attention were a prevalent feature in the ADHD group. Current collaborative projects include work (with K. Cornish, McGill University) on relationships between cognitive/behavioural dysfunction (assessed using the TEA-Ch), spatial bias and candidate genetic markers.

A6.3 Persistent vegetative state

Scientific direction: Owen (5%)

Despite converging agreement about the definition of persistent vegetative state, recent reports have raised concerns about the accuracy of diagnosis in some patients, and the extent to which, in a selection of cases, residual cognitive functions may remain undetected. Objective assessment of residual cognitive function can be extremely difficult since motor responses may be minimal, inconsistent, and difficult to document. In the absence of motor output, functional neuroimaging with well-documented paradigms may allow the imaging of specific task-related cortical activation, and provide one means of assessing cognitive processing. Owen, working with the clinical team at the WBIC and Professor D. Menon of Department of Anaesthesia, Cambridge, has investigated strategies for using PET in this role, the clinical condition of many patients precluding MRI. Functional neuroimaging in two persistent vegetative cases has produced extremely encouraging results, leading to publications in The Lancet (Menon et al., 1997), Trends in Neurosciences (Menon et al., 1999) and Neurocase (Owen et al., in press), as well as significant media coverage on television, radio and in print. In these two patients, clear and predicted regional cerebral blood flow responses were observed during well-documented activation paradigms (face recognition; see Figure A6.1, and speech perception) which have been shown to produce specific, robust and reproducible activation patterns in normal volunteers. Some months after scanning, both patients made a significant recovery suggesting that imaging in this patient group may provide novel information about likely outcome. In spite of the multiple logistic and procedural problems involved, these results have major clinical and scientific implications and provide a strong basis for the systematic study of possible residual cognitive function in these patients.

A6.1: Surface rendered normalised PET data from the familiar face perception task superimposed on standard 3D-rendered magnetic resonance template. Both for control and patient, strong right hemisphere activation is seen in the fusiform gyrus.



AWARDS AND HONOURS

In 1998, Dr R. P. Carlyon was was elected a Fellow of the Acoustical Society of America. His article co-authored with D. M. Bishop, J. Deeks, and S. Bishop (see publication list) won the Journal of Speech, Language, and

Hearing Research's Editors' Award for 1999. Dr J. Duncan was made an Honorary Professor at the University of Wales in 2000, was invited with six others to form the Scientific Advisory Board of MIT's McGovern Institute in 2002, and became Secretary of the International Association for the Study of Attention and Performance in 2002. In 2000 he gave the British Psychological Society's Broadbent Lecture. From 1995 to 2000, Dr A. M. Owen was Vice-President of the International Society For Behavioural Neuroscience. Dr I. H. Robertson was made Visiting Professor at University College London in 1997.

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TRANSFER TO HEALTH SERVICE

There has been a strong emphasis on the transfer of research findings relevant to rehabilitation and assessment to the NHS. Robertson and Manly have presented numerous workshops and clinical lectures to NHS professional groups in both community and hospital settings and have been active in training and post-graduate programmes of clinical psychologists. The ongoing programme of clinical workshops at the Oliver Zangwill Centre draws heavily upon the Unit's work. Assessment instruments for adults and children derived from studies in the Attention Group are now very widely used throughout the UK (and internationally). The work of Robertson and colleagues on limb activation therapy for unilateral neglect has now been widely adopted within stroke medicine services and the recent work of Robertson, Duncan and colleagues on Goal Management Training is having increasing influence on services, forming a central part, for example, of the programme for remediation and management of dysexecutive deficits at the Oliver Zangwill Centre.

EXTERNAL GRANTS

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3 COGNITION AND EMOTION GROUP PROGRESS REPORT

Overview

The aims of the Cognition and Emotion programme are 1) to increase basic understanding of the representation, elicitation, maintenance, and control of emotion, at neurobiological, cognitive, and computational levels of explanation, and 2) to apply that understanding to the analysis and treatment of disorders of emotion. Research spans a range from the detailed analysis of perceptual mechanisms of emotion recognition, using neuroimaging, neuropsychological, and cognitive methodologies, through to the development of novel therapeutic interventions and their evaluation in clinical trials. This breadth of inquiry is co-ordinated within multi-level theoretical frameworks developed by our group (e.g. Mathews & Mackintosh, 1998; Power & Dalgleish, 1997; Teasdale & Barnard, 1993). It is increasingly recognised that such frameworks are necessary for a comprehensive understanding of the multiple interacting processes that contribute to emotion production and control. Our research has generated a wealth of specific findings. Here, we preview some of the more important general conclusions that emerge from our studies. These conclusions offer guidance for deepening basic understanding, formulating further research, and improving patient care.

Neuroimaging and neuropsychological studies conducted in Projects CE1 and CE6 have produced critical new evidence converging on the conclusion that multiple brain systems interact in processing emotional information. In summary, some brain systems (e.g. amygdala, insula) have been shown to be involved in processing affective stimuli associated with specific basic emotions while others (e.g. medial frontal cortex) appear to be involved in a range of emotions, drawing on multiple sources to compute more complex emotional and social meanings. Yet others (e.g. anterior cingulate cortex and dorsolateral frontal cortex) are concerned with higher level control of both emotional and non-emotional processing. Differences in neurotransmitter receptor densities in some of these systems have been shown to correlate with trait differences in emotionality, providing a new means of testing theories of how emotions and personality traits are related. The propensity to experience emotions thus depends on the outcome of interactions among several different brain systems. The co-existence of specificity and generality of emotion-related brain functions is precisely what our multi-level analyses of emotion predict, and reinforces our strategy of combining detailed investigation of individual component systems, with the development of frameworks that specify how those components interact.

Work on recognition of emotional expression (Projects CE2 and CE6) illustrates how the detailed investigation of particular component systems can yield an elegantly simple model that captures key features of a range of functions. Building on earlier work on recognition of facial identity, research in the reporting period has shown that multidimensional principal component analysis provides compelling models. These can account not only for recognition of identity, but also of emotional expression, gender, the dissociation of identity and expression recognition, effects of emotional intensity, and the configural nature of expression processing. The success of this work indicates the potential fruitfulness of focusing analysis at the level of component systems.

At the same time, the strategy of focusing investigation on component systems and subsystems needs to be complemented by analyses that focus on the patterns of interaction between subsystems that support more complex functions. This is a formidable challenge. Project CE3 describes the early stages of development of a radically new approach to computational modelling which has explored the distributed control of exchanges between component subsystems within a wider, distributed system. This modelling work has been complemented by empirical work in both clinical and non-clinical populations. This has shown that important aspects of central executive function can be understood in terms of changes in the patterns of interaction between subsystems, rather than deficits or anomalies in the subsystems themselves. This work validates the potential usefulness of this unique approach to computational modelling. It indicates that we can now move forward to model further aspects of the exchanges between subsystems that our models suggest are of central importance in cognitive-affective function.

The interaction of automatic affective and controlled cognitive processing is particularly important in understanding the maintenance of affect. Project CE4 addressed instances of such processes associated with vulnerability to anxiety and depression, such as selective attention to threatening information, and perception of the more negative meanings of ambiguous events. These processes have the effect of making potential threats more intrusive, and in this way can maintain negative emotions. New evidence shows that opposing positive biases occur in healthy people, but are not present in anxious patients. A similar failure of positive bias can be induced experimentally, producing symptoms characteristic of anxiety disorders. In healthy individuals, task-irrelevant aversive stimuli are typically easily ignored, but work in this project has revealed that those vulnerable to negative affect are less able to disengage from such stimuli, and to inhibit or forget unwanted aversive meanings. These findings show that stable individuals are able to inhibit mildly aversive information, but that inhibition failure is associated with vulnerability to anxiety or depression, and that such processing causes congruent changes in affective symptoms. In demonstrating the importance of such failures of disengagement and inhibition, these studies point to a need to shift the emphasis in existing explanatory models. Rather than attempting to understand emotional disorders solely in terms of excessive activation of dysfunctional representations and processes, such accounts also need to recognise more clearly the importance of failures of appropriate inhibition.

Self-perpetuating emotion-related cognitive biases, such as those studied in Project CE4, have figured prominently in the multi-level analyses of emotional disorders developed by our group. Given the weight attached to these biases in the maintenance of emotional disorders, such as major depression and generalised anxiety, it is important also to understand their role in the initial onset of disorder, To this end, Project CE5 included extensive investigations of emotion-related cognitive biases in children with emotional disorders, many of whom were experiencing their first episodes, and in children who were at risk for disorder but who had not yet experienced an onset of the disorder. Findings demonstrated a pattern of disorder-specific cognitive biases that were very similar to those found in adult disorders, and that, in some cases could be shown to pre-date onset of disorder. These findings are important in suggesting that the identified self-perpetuating cognitive biases may be risk factors contributing to the initial onset of emotional disorders, rather than being primarily aftereffects of the experience of the initial episode.

Neurosurgical interventions on the intact human brain offer a rare opportunity to investigate the neural substrates of emotional disorder with the precision that is more usually associated with studies of experimentally induced lesions in animals. Project CE6 took advantage of such an opportunity in studying the effects of stereotactic subcaudate tractotomy for the relief of treatment resistant depression. The findings indicated a remarkable degree of specificity in the effects of this operation on neuropsychological measures. These effects were specific to reductions in patients' sensitivity to negative feedback information. This reduced sensitivity was shown only by patients who benefited clinically from the operation, and was not shown by either operated patients who failed to benefit from the operation, or by patients who did not receive the operation but whose depression improved as a result of pharmacotherapy. Such specificity is consistent with a causal role for reduced sensitivity to negative feedback in patients' clinical improvement, and for a role for heightened sensitivity in the maintenance of chronic depression. This study demonstrates the potential utility of this investigative strategy, as a way of elucidating simultaneously both the nature of depressive psychopathology, and the role of specific regions of the human brain.

Our multi-level analyses of emotional disorder implicate self-perpetuating cognitive-affective processing configurations in the moment-to-moment dynamic maintenance of states such as generalised anxiety and major depression. A crucial test of such models is the extent to which particular cognitive processing styles, that we believe play a causal role in perpetuating aversive emotional states, can be experimentally controlled. Project CE7 has shown that a threat-related attentional bias, of the kind assumed to maintain generalised anxiety, can be induced to previously neutral stimuli by associating them with threatening meanings, without participants' awareness. Further, practice in accessing negative meanings of ambiguous material was shown to lead to a related bias in processing new ambiguous information, together, most interestingly, with the development of a tendency to respond with anxiety to such information. These findings provide the first evidence that processing biases can indeed be a cause of anxiety. In major depression, brief attentional manipulations were found to reduce overgeneral memory, a characteristic feature of individuals prone to depression. These findings are consistent with the idea that overgeneral memory, like other features of depression, is dynamically maintained by self-perpetuating processes that can be interrupted, rather than an enduring trait-like feature, as was generally previously assumed. Further, this work has characterised two distinct modes of self-attention, one associated with perpetuation of depressive cognition, the other with its amelioration. Thus, laboratory-based manipulations can bring cognitive processes characteristic of emotional disorders, under experimental control. By manipulating the form of these processes, we have shown that they have causal effects on symptoms of emotional disorder. Further, this work has identified potential therapeutic processes for inclusion in clinical treatments.

An important motive for our more basic research on the interaction between cognition and affect in normal and disordered emotion has been to provide a firm basis for the development of new and more effective approaches to the treatment and prevention of emotional disorder. Project CE8 illustrates how our theoretical and experimental studies led to a radically different way to understand the effectiveness of an existing treatment for depression, cognitive therapy, which then provided the basis for the development of a new cost-efficient programme to prevent relapse in recurrent depression. Specifically, we gathered support for our hypothesis that cognitive therapy works through implicitly changing the mode of processing of negative thoughts and feelings, rather than through changing belief in the content of negative thoughts, as is generally assumed. This hypothesis guided the development of a programme explicitly designed to achieve the same ends as cognitive therapy, through systematic training in the control of modes of attention. In two clinical trials, we showed that this intervention, firmly rooted in theoretical and experimental work conducted within the Cognition and Emotion group, was highly effective in reducing relapse in recurrent depression, and did so in a way consistent with the processes that we had specified. This work validates our strategy of developing new approaches to patient care grounded in our basic research on cognitive-affective interaction.

Project CE1: Affect-related representations.

Scientific Direction: Calder (5%), Lawrence (70%), Mathews (20%), Teasdale (5%).

MRC-supported scientists: Murphy (100%)

Grant-supported scientists: Bishop (15 months, 100%), Potts (from January '02, 100%).

Research support: Green (5%), Keane (5%), Yiend, (20%).

The multi-level information processing analyses of emotion developed within the Cognition-Emotion group identify both sensory/perceptual and cognitive/interpretative levels of representation in the generation and regulation of affect, and in the interaction of cognition and emotion. The aim of project CE1 is to use functional neuroimaging and complementary techniques to identify the neural substrates of these interacting levels in cognitive-affective processing. Findings suggest that some brain systems are involved in processing specific types of sensory/perceptual emotional stimuli (e.g. amygdala, insula), while others (e.g. medial frontal cortex) probably draw on multiple sources of information to compute more complex emotional meanings. Yet other systems (e.g. dorsolateral frontal cortex) are concerned with higher level control of both emotional and non-emotional processing.

CE1.1 The cognitive generation of affect

The Interacting Cognitive Subsystems (ICS) framework (Teasdale & Barnard, 1993) suggests that the cognitive generation of affect depends on the integration of propositional meanings with perceptual input, to form schematic affective representations. Teasdale, in collaborative work at the Institute of Psychiatry, has conducted fMRI studies aimed at identifying brain networks mediating such cognitive generation of affect. These studies compared the activation elicited by presenting pictures and captions combined so as to represent a meaningful emotional event, or in a re-combined form so that they no longer meaningfully cohered. This methodology controls precisely for all aspects of stimulus materials other than the extent to which captions and pictures cohere. It follows that comparison of coherent and non-coherent caption-picture pairs identifies structures mediating the specifically meaning-related contribution to the generation of affect. Using this approach, Teasdale, Howard, Cox, Ha, Brammer, Williams & Checkley (1999) identified medial prefrontal networks related to the processing of schematic-level meanings and the cognitive generation of positive and negative affect. Networks activated were similar to those reported in other affect-elicitation imaging studies (see CE1.3); the importance of this study is the precision with which the contribution of complex emotional meanings to affect-elicitiation can be specified.

A subsequent study using the same methodology (Kumari et al., in press) replicated these findings for normal subjects, and compared them with treatment resistant depressed patients. Compared to the controls, patients showed significantly less activation in the identified medial prefrontal networks to positive caption-picture pairs, suggesting deficits in the processing of cognitively generated positive affect in treatment resistant depression.

CE1.2 Eye gaze processing

The direction signalled by another person's eye gaze not only carries information about where the other person is looking (i.e., attentional cues), but also that something, or someone, has captured the gazer's attention. Consistent with the latter, Baron-Cohen (1997) has proposed that the interpretation of gaze plays an important role in a normally functioning theory of mind (ToM) system. Calder validated this role by showing that a meta-analysis of functional imaging research demonstrated that both ToM and eye gaze tasks engaged a similar region of posterior superior temporal sulcus (STS) (Calder et al., 2002). In addition, he noted that a second, more prominent brain region associated with ToM, the medial prefrontal (MPF) cortex, had not been identified by eye gaze research. In collaboration with Lawrence, Calder identified methodological issues that might account for the absence of MPF activation in these experiments. He then conducted a PET study that controlled for these factors and addressed the neural correlates of processing direct and averted gaze (Calder et al., 2002). The results showed that the MPF regions associated with ToM were indeed involved in processing gaze, but particularly averted gaze. Moreover, because participants were not explicitly asked to attend to the faces' gaze, the study demonstrates that simply viewing a face with averted gaze is sufficient to engage the mechanisms involved in ToM. This provides the first demonstration that the mechanisms involved in processing another person's mind state are engaged automatically. The MPF regions involved were very similar to those implicated in the cognitive generation of affect in CE1.1, consistent with a role for these brain regions in the processing of affect-related implicit meanings, and contributions from such meanings to gaze-related affect generation.

CE1.3 A novel imaging meta-analytic approach to understanding the structure of neural emotion space

The conclusions that can be drawn from any single functional imaging experiment are, necessarily, limited. To overcome this difficulty, Murphy, Nimmo-Smith & Lawrence (Lawrence & Murphy, 2001; Murphy, Nimmo-Smith & Lawrence, submitted) have applied novel statistical techniques to the meta-analysis of very large numbers of functional imaging experiments. Using a variant of the Kolmogorov-Smirnoff statistic, they examined the distribution of patterns of activation foci in functional imaging experiments, and how these distributions relate to models of the neural representation of emotions. Using data pooled from over 100 experiments, they tested predictions made by categorical (e.g. basic emotions) versus dimensional (e.g. approach/avoidance; valence/arousal) frameworks. In support of basic emotions accounts, the distribution of activation foci associated with discrete affects (fear, anger, disgust) were significantly different from each other, and from happiness and sadness. In contrast, the activation peaks for happiness and sadness were not different from each other. In addition, fear, disgust and anger activations were maximal bilaterally in regions which, when damaged, are associated with selective deficits in processing these emotions (fear - amygdala, disgust - insula, anger - ventral frontal cortex - see CE6); whereas happiness and sadness activations tended to cluster in the anterior cingulate. Activation of anterior cingulate cortex was associated with the majority of emotions, with the exception of disgust, suggesting that this region plays a generic role in the processing of a range of affects - consistent with multi-level representation of emotion. There was also some support for a differentiation of emotions in terms of associated action tendency (approach / avoidance), but no evidence for coding based on valence or arousal dimensions.

CE1.4 Emotional associative learning

The study of reward learning in animals has revealed an interrelated set of limbic and cortical structures involved in reinforcement and motivation. Emotional associative learning in humans has not yet been much investigated from a similar neuroscientific perspective. Conditioned place preference is one of the most common procedures for assessing stimulus-reward associative learning in animals, and Johnsrude, Owen, Zhao, & Whitney (1999) have developed an analogous procedure for use with people. Using this procedure, Johnsrude, Owen, White, Zhao & Bobhot (2000) have shown that unilateral removal of the temporal lobe, including the amygdaloid region, in humans (for the treatment of epilepsy), abolishes either the formation or expression of such conditioned preferences. In contrast, patients with unilateral frontal-lobe removals were unimpaired. This result provides clear evidence that, in humans as in other animals, reward-related learning critically depends on a circuit involving inferotemporal cortex and the amygdaloid region.

CE1.5 Interactions of emotional and cognitive control systems in the brain

Interactions between emotional processing and cognitive control systems are assumed to play a central role in the maintenance and regulation of affect. Mathews & Mackintosh (1998) proposed that threatening representations (of stimuli such as fear-related pictures) receive additional activation from a threat evaluation system (involving the amygdala complex), so that they are more likely to capture attention. Such activation may be inhibited, if it would conflict with other current goals, by competing activation of task-related representations from a control system, involving medial and dorsolateral areas of the frontal cortex. Mild emotional distracters may thus be ignored, and only more severe threats will disrupt attention to ongoing tasks (Mackintosh & Mathews, in press). Unintended attention to threatening distracters, which characterizes individuals vulnerable to anxiety states, can thus arise due to a lower response threshold in the threat evaluation system, and/or relatively weak inhibition by the control system.

Using fMRI, Mathews and Lawrence investigated the neural correlates of encoding manipulations on threat related material, in high and low anxious subjects, to test predictions made by the above model. Subjects viewed sets of pictures without specific instructions, and other sets while performing tasks: either judging if the current picture is more fear-inducing than the previous one (emotional task); or if it required more preparation by the photographer (non-emotional task). Findings so far are that threatening pictures provoke more activation in the primary visual cortex, parietal regions, and amygdala than neutral pictures. A parallel psycho-physiological study employed a noise-induced startle response to index amygdala activation. Startle magnitude was augmented when viewing threatening versus neutral pictures, and this difference was enhanced by judgements of fear, but was abolished by the non-emotional judgement task. These findings suggest that affect-related amygdala activation can be modulated by conscious cognitive control.

In collaboration with Bishop, Brett and Duncan (attention group), Lawrence conducted an event-related fMRI study to investigate the role of different prefrontal cortical structures in the processing of emotional material.

Using a task which requires matching pairs of houses in the presence of emotional distractors (fearful faces), combined with a trial structure manipulation (frequent versus infrequent distractors) known from previous work to manipulate levels of cognitive control, this study demonstrated a role for the anterior cingulate (affective division) in detecting the presence of response conflict engendered by the presence of emotional distractors. In contrast, the dorsolateral prefrontal cortices were involved in implementing attentional control. Differences in dorsolateral prefrontal cortex were also seen as a function of anxiety levels. This work showed, for the first time, that different structures (anterior cingulate and lateral prefrontal cortex) play dissociable roles in control of emotional material (Bishop, Duncan, Brett & Lawrence, in submission). Further, it showed that areas already known to be involved in controlling attention in non-emotional tasks (the anterior cingulate and dorsolateral frontal cortex) are also employed when controlling response to emotional information.

CE1.6 Individual differences in affective style and temperament and their neurobiological correlates

Better understanding of the neurobiological substrates of stable individual differences in temperament and affectivity is centrally relevant to improved models of psychopathology. One of the most powerful theoretical frameworks for explaining such individual differences and their relation to emotion systems is the reward sensitivity theory of Gray (Gray, 1982). Gray's model postulates two major dimensions of temperament, anxiety and impulsivity, that represent individual differences in the sensitivity of two neural systems involving processing of aversive (Behavioural Inhibition System, BIS) and appetitive (Behavioural Activation System, BAS) cues, respectively. Certain forms of psychopathology can be characterized in relation to these major axes of personality variation (Pickering & Gray, 1999). For example, a link between the positive symptoms of schizophrenia and BAS function has been proposed (Pickering and Gray, 1999) and clinical anxiety is thought to be related to high levels of BIS activity.

Lawrence, in collaboration with Goerendt, Rabiner, McGowan, Brooks and Grasby at MRC Clinical Sciences Centre, London, have shown that individual differences in serotonin 5HT1a receptor densities in the hippocampus and amygdala are associated with individual differences in BIS function (as measured by the difference between scores on extraversion and neuroticism), but not with neuroticism or extraversion per se (Rabiner et al., 2002a and unpublished data). These data are consistent with Gray's model.

An intriguing finding from these initial studies was that 5HT1a receptor levels were associated also with scores on the lie scale from the Eysenck Personality Inventory (Rabiner et al., 2002a). Although initially thought to be a measure of false but socially desirable responses, it has been known for some time that this factor is in itself a substantive aspect of personality, and individual differences in this trait (sometimes called defensiveness) have been related to lifetime risk of psychopathology. Rabiner et al., (2002b) have replicated this finding in a new group of individuals. The finding of a relationship between scores on the lie factor and 5HT1a receptor levels has implications for conceptualisations of a serotonin-linked trait as well as factors predisposing to risk of affective disorder, and suggest revisions to reward sensitivity theory will be required.

Gray's model also predicts that individual differences in BAS system function will relate to indices of dopaminergic activity. Lawrence, together with Goerendt and Brooks, MRC CSC, have used [18F]Fdopa and [11C]Raclopride PET to measure individual differences in dopamine uptake and D2 receptor status, and have found that measures of impulsiveness are correlated with ventral striatal activity, but only in male participants.

In addition, they have used H2[15]O PET to map the structures involved in processing cues thought to activate the BAS (financial rewards), and the modulation of these structures by dopamine neurotransmission (studies in Parkinson's disease). This work has shown that ventral fronto-striatal circuits mediate BAS function, and these structures are less activated in unmedicated PD patients, especially those showing symptoms of apathy, but can be restored by treatments that increase dopamine levels. In addition, behavioural work has shown that these circuits mediate the incentive motivational (speed enhancing) effects of monetary rewards.

A neuropsychological study found that individuals with anorexia nervosa, a profound disorder of appetitive function, show highly selective deficits in reward-based learning, consistent with a rather specific deficit in a BAS system. In contrast, they show no impairment on difficult pattern recognition memory tasks associated with medial temporal lobe function (Lawrence, Dowson, Foxall, Summerfield, Robbins & Sahakian, in press).

Gray's model predicts an association between the neural systems implicated in BAS system function and the neurobiology of positive schizophrenic symptoms (Pickering & Gray, 1999). In collaboration with McGowan and Grasby (MRC CSC, London), Lawrence has used PET imaging (blood flow and [18F]Fdopa to image dopamine function) to test this hypothesis. In line with Gray's theory, schizophrenic patients showed increased [18F]Fdopa values in the ventral striatum, related to their degree of positive symptomatology. In addition, [18F]Fdopa values were correlated with performance on tasks requiring the use of stored regularities to guide behaviour (such as verbal fluency) (McGowan, Lawrence & Grasby, 2001b, submitted).

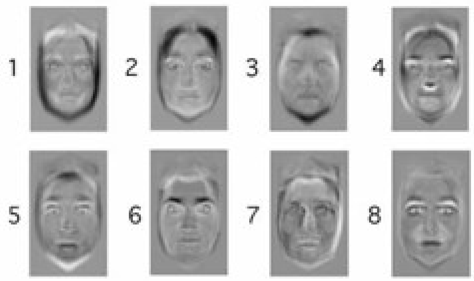
Project CE2: Recognition of emotion

Scientific Direction: Calder (55%).

Research support: Keane (55%).

The majority of research in facial expression processing has focused on the communicative value of facial expressions, and few studies have investigated the perceptual processes preceding this stage. As a result, there is no detailed model of facial expression recognition. Project CE2 addressed the perceptual mechanisms underlying the recognition of facial affect, with a view to developing a model of facial expression processing. The resultant multidimensional framework, based on principal component analysis (PCA), can account for all of the phenomena discussed below.

Figure 1: The first eight eigenvectors (eigenfaces) extracted from a PCA of the Ekman and Friesen (1976) pictures of facial affect. The eigenvectors have the same dimensionality as the original starting images so they can be displayed as visual images that have a ghost-like facial appearance. Note that the eigenvectors clearly capture aspects of the different expressions.



CE2.1 Front-end coding of facial expressions

It is generally agreed that facial identity recognition (who the person is) and facial expression recognition (what they are feeling) share the same front-end (perceptual) system. Previous research has shown that a principal component analysis (PCA) of the visual information in faces provides an effective front-end account of facial identity processing (Burton, Bruce, & Hancock, 1999). Hence, two critical questions are whether PCA can also support the recognition of facial expressions, and whether it provides a suitable means of coding a face's identity, expression, and sex within a single dimensional framework. Calder has addressed these issues by submitting the pixel intensities of pictures of facial expressions from the Ekman and Friesen (1976) series to a PCA (Calder, Burton, Miller, Young, & Akamatsu, 2001a) (Figure 1). The results showed that PCA provides a highly effective means of coding all three facial attributes. For facial expressions, the correct recognition rates and false positives derived from the principal components were well matched to human performance. In addition, the model exhibited properties of two competing accounts of facial expression processing (dimensional and category-based models), providing a means of reconciling what were generally perceived to be distinct theoretical accounts. Consistent with research showing that facial identity and facial expression recognition can be selectively disrupted, Calder found that cues to identity and expression were coded by largely separate sets of principal components. A similar dissociation was found for expression and sex, while, consistent with recent cognitive research, identity and sex were coded by largely overlapping sets of PCs (Ganel & Goshen-Gottstein, 2002). This research shows that linearised compact coding of human faces provides a highly plausible account of the psychological data.

CE2.2 Configural coding

It is well established that configural information (the relationships between facial features) plays an important role in coding a face's identity. However, its contribution to facial expression recognition is less well understood. In fact, some researchers have suggested that facial expressions are processed in a part-based (non-configural) manner (Ellison & Massaro, 1997). Calder addressed this issue using a composite paradigm (Calder, Young, Keane, & Dean, 2000d). Participants were slower to identify the expression in either half of composite facial expressions: that is, faces in which the top half of one expression (e.g., anger) was aligned with the bottom half of another (e.g., happiness) to create a novel expression configuration relative to a noncomposite control condition in which the two face halves were misaligned. These findings support the role of configural coding in facial expression recognition, and parallel the composite effect for facial identity (Young, Hellawell, & Hay, 1987). However, Calder also showed that the identity and expression effects operate independently of one another (i.e., the configural cues to these two facial attributes are qualitatively different). This research complements the findings of the PCA (see above) which showed that identity and expression are represented by separate principal components. In line with this observation Cottrell (California, San Diego) and Calder have shown that PCA provides an effective model of Calder's composite data (Cottrell, Branson, & Calder, 2002).

CE2.3 The representation of facial expressions

Facial expression recognition has been discussed in terms of two types of models. In category based systems, each expression is identified by activating a discrete representation. By contrast, in low dimensional accounts, facial expressions are identified by judging their values on two, or three continuous dimensions. These models have been applied to the recognition of emotion in general. However, as illustrated by the principal component analysis of facial expressions discussed above, they are also competing candidates for the perceptual representation of facial affect. To address this debate, Calder conducted a number of experiments using photographic-quality morphs (blends) and caricatures of facial expressions prepared using a computer-based procedure.

CE2.3.1 Categorical perception

Two studies used a categorical perception paradigm (Harnad, 1987) to address participants' perception of morphed facial expression continua ranging between pairs of facial expressions (e.g. anger and disgust; Calder, Young, Perrett, Etcoff, & Rowland, 1996a; Young et al., 1997). Results showed that all morphed images were consistently identified as the expressions at either end of the relevant continuum, with a sharp category boundary at the middle. In addition, pairs of morphs that straddled the category boundary were better discriminated than pairs of equal physical magnitude from either side of the boundary. Calder and Young have argued that these findings are consistent with the view that facial expressions are coded as discrete categories. In his work on PCA, Calder has proposed that facial expression categories can be viewed as clusters of vectors in a multidimensional space, with each cluster representing an attractor state for one facial expression (Calder et al., 2001a). Hence, categorical perception is consistent with a multidimensional account of facial expression coding. This research has also led to the production of a neuropsychological test of facial expression recognition (The Emotion Hexagon) that uses morphed facial expressions. To date, the test has been used in a number of studies, including those in CE6.

Figure 2: An example of a caricature (+50%) and anticaricature (-50%) image of an afraid facial expression. The images were produced by exaggerating (caricature), and reducing (anticaricature), the differences between the original afraid expression (0%) and a picture of the same model posing a neutral expression (left).

CE2.3.2 Emotional intensity

An important factor that distinguishes facial identity and facial expression is that the latter vary in intensity. Calder investigated the intensity issue using photographic-quality caricatures of facial expressions. Caricatures were produced using a computer graphics technique that exaggerated the physical differences between a particular facial expression (e.g., fear) and a picture of the same model posing a neutral expression. Similarly, anticaricature expressions were produced by reducing these differences (Figure 2). Subjects were significantly faster to recognise caricatured expressions relative to the original undistorted images, whereas anticaricatures produced slower recognition rates (Calder, Young, Rowland, & Perrett, 1997). An additional study showed a positive linear relationship between level of caricature and rated emotional intensity – but only for the emotional scale corresponding to the emotion displayed (i.e., fear caricatures were rated as expressing more fear, but not as more disgust, anger, etc.; Calder et al., 2000c). Caricatured expressions have provided a valuable stimulus material for Calder's collaborative functional imaging projects (see CE6). These studies mirror the findings discussed above by showing that caricatures of fear and disgust engage different brain regions, with changes in neural activity being positively related to level of caricature (Morris et al., 1998; Morris et al., 1996; Phillips et al., 1997; 1998). Calder has shown that caricature effects for facial expressions are best accounted for by an exemplar-based model of facial expression coding, analogous to the PCA architecture discussed above (Calder et al., 2001a; Calder et al., 2000c). In such a system, each expression category is coded as clusters of exemplars (vectors) in multidimensional space, and caricaturing operates by shifting the expression along the vector.

Summary: This research programme has addressed the perceptual processing of facial expressions from front-end analysis through to the point of representation. The results demonstrate that a multidimensional system based on a form of linear encoding analogous to PCA, provides a suitable metaphor for processing facial affect. Moreover, this single PCA-based system provides a model of coding a number of facial attributes (i.e., facial identity, expression, and sex). In addition, it can account for the dissociable effects observed for facial expression and facial identity processing (e.g., different configural cues for expression and identity), and single route coding of identity and sex (Ganel & Goshen-Gottstein, 2002). The same multidimensional metaphor also provides a suitable account of the effects of categorical perception, caricature, and configural processing described.

Project CE3: Multi-level representation and processing dynamics

Scientific Direction: Barnard (90%).

Research support: Ramponi (90%).

MRC-supported students: Battye (3 years, 100%).

Grant-supported students: Tavares (1 year, 100%).

Multi-level theories focus on different types of representation and the parts they play in the generation and maintenance of affective states. The need for theories of this class, their properties, and their potential for linking information processing to neural level analyses have been reviewed (Teasdale, 1999a). Such theories provide an explicit basis for the distinction between a traditionally cognitive, or propositional, level of representation, within which emotion-related material may be discussed rationally, and non-conceptual levels of representation and meaning that are directly linked to affect.

The Interacting Cognitive Subsystems architecture (ICS) is an example of a multi-level theory that is formulated with sufficient precision to support both empirical studies and computational research. It views central executive functions as an emergent property of reciprocal exchanges between one subsystem that represents specific meanings as propositions and another subsystem that represents implicational meaning. Implicational meaning is cognitive-affective and takes the form of abstractly encoded schematic models of self, others and the world. These bring together the products of propositional cognition and the products of sensory processing, including body states. Exchanges between two levels of representation act as a real-time control loop for ideation and memory access, without theoretical reference to general-purpose resources such as a unitary central executive or a limited capacity working memory system (Barnard, 1999).

As a system-level approach, exchanges among levels of representation within ICS can operate in a number of alternative configurations. The configurations differ in the parts played by processes in the propositional and implicational subsystems (Barnard, 1985). A process can operate in automatic mode, relying solely on its immediate input to generate an output. Alternatively, a process can be re-configured to use an extended representation of recent input (buffered mode), or it can access longer-term regularities stored in memory (record access). Propositional-implicational exchanges can be co-ordinated by buffering propositional meanings, and their specific content, or by buffering schematic meanings with their more generic properties. In the propositional mode, internal attention and experience is focussed on specific meanings, while in the implicational mode, it is focussed on more generic, and potentially affectively charged meanings. As with many other theories, dysfunctional ideation is assumed to call upon abnormal schematic models of self, others and the world. What ICS adds is the hypothesis that key properties of normal and dysfunctional processing arise from an interaction between schematic models and the alternative modes in which they are processed while attending to meaning or retrieving it. This dynamic approach led to what has now become an influential account of depression (Teasdale & Barnard, 1993). It links depression to a state of interlocked processing between two levels of meaning in which attention is predominantly focussed on the propositional meanings that are generated by depressogenic schematic models. The general hypothesis is that executive control of normal and dysfunctional ideation depends upon models and modes. Specific control parameters, such as the salience and extent of discrepancies, or rates of change in information content, are hypothesised to determine how use of modes is dynamically co-ordinated over time.

In the current reporting period specific empirical projects have investigated how schematic models and modes influence the executive control of ideation in healthy volunteers and in patient groups. Theoretical work has tackled the difficult problem of how to resolve the computational issues that must be addressed when modelling complex systems with distributed rather than centralised control, and several forms of novel computational approaches have been developed. Additional theoretical work extending the ICS account from depression to other psychopathologies is described in CE5.

CE3.1 Attention to meaning in healthy volunteers

In everyday life there is natural variation in the extent to which we attend to detailed aspects of meaning. When asked a question like "How many animals of each kind did Moses take into the Ark?" many people will answer "Two" - not noticing that the relevant Biblical figure was actually Noah (Erickson & Mattson, 1981). Both Moses and Noah fit the same schema and this kind of phenomenon can be taken to index the extent to which respondents adopt an executive mode in which they analyse propositional meaning, or rely on more generically encoded schemata or models. The Moses illusion reflects the fact that much useful ideation can occur simply by glancing at schematic models in implicational mode. If no global discrepancy in meaning is detected from the glance, then a response can be generated without switching to the more time-consuming propositional mode required to take a detailed look at specific meanings. As a background for studies of patient populations, we investigated this type of phenomenon in normal healthy volunteers using two paradigms, one involving question-answering and the other involving watching rapidly presented lists of words belonging to a generic category and detecting targets that belonged to a semantically specific category.

CE3.1.1 Modes, schematic models and question-answering

Laboratory studies of executive function in healthy volunteers are likely to have over-estimated the extent to which ideation works in the analytic propositional mode, and underestimated how use of schematic models constrains understanding. Most tests take repeated measurements on similar problems and thus encourage participants to develop special-purpose executive strategies to minimise error. We asked single unexpected questions requesting a single large number in between two bounds (e.g. Can you please give me a random number between one million and ten million?). Small differences in question phrasing invoked very different distributions of responses. These allowed us to determine the generic features of numbers, such as their magnitude, parity, and complexity, that had been attended to, and hence we could infer what schematic models had been activated by the different questions (Scott, Barnard & May, 2001). As with the Moses illusion, we found that volunteers often failed to focus their attention on the relevant bounds, and did not check their responses prior to generating them. They frequently erred by reporting numbers outside the requested range. A follow up study also varied question phrasing but this time varied processing load by increasing the length of the number sequence to be generated. Here, we found that executive error rates in healthy populations occurred with 50% of the volunteers under conditions of high load (Barnard, Scott, & May, 2001). In both studies we demonstrated that the kind of executive errors often committed by frontal or manic patients can be understood as phenomena that also occur within the range of normal processing, albeit perhaps at the extreme of that range (see also CE5.2.2). Both the occurrence and nature of, these errors can be understood as resulting from attention primarily being paid to generically encoded schematic models rather than propositional details.

CE3.1.2 Modes of processing meaning and the Attentional Blink.

In another series of studies, we developed a novel variant of the attentional blink (AB) paradigm (Raymond, Shapiro & Arnell, 1992). We asked volunteers to detect an instance of a semantic category (jobs/occupations) in rapid serial visual presentation where most of the words belonged to a category (nature words) unrelated to the target. Our procedure ensured that volunteers could only determine what was and was not a target by processing meaning. If the sequence included non-target distractors, (e.g. miser) that were related in meaning to a subsequent target, then report of that target was substantially impaired. While evaluating the precise meaning of the distractor, they missed the target much more frequently than in a control condition with no distractor. Only minor impairment occurred in response to a category change unrelated in meaning to the target category. To have an effect the distractor had to be semantically salient. We used a sophisticated form of statistical semantics called Latent Semantic Analysis (Landauer & Dumais, 1997) to index semantic relatedness and to eliminate a simple priming explanation. The results supported an explanation in which an initial glance at implicational meaning marks an item as salient and triggers an extended look at its propositional meaning (Barnard, Scott, Taylor, May & Knightley, submitted). This demonstrated that AB onset and duration could be taken to index the time course of processing generic and specific meanings. It also led to a more controversial conclusion. Results obtained in the standard AB paradigm with coloured letters are now potentially open to explanation based on purely semantic mechanisms.

CE3.2 Attention to meaning in depressed, manic and anxious states

Taken together, the question-answering and AB paradigms provided evidence that modes adopted when paying attention to two levels of meaning are open to measurement and varied systematically in healthy volunteers. Since implicational meaning encompasses affect, the same tasks can be used to investigate the effects of different emotional states on the executive control of attention to meaning as a function of hypothetical parameters such as rates of information change or personal salience.

CE3.2.1 Executive modes in manic and depressed states.

In depressed states, Teasdale & Barnard (1993) argued that an analytic, propositional mode is preferentially adopted when processing negative self-models. Repeated generation of the same thought also implies a low rate of change in generic self-models or representations, with rather more moment to moment change in specific propositions. We have also argued that a more experiential, schematic mode is adopted in mania where high rates of change in generic representation occur in the form of flights of ideas (Barnard, in press). Our theoretical analysis argued that attention moves to the level of meaning with higher rates of change. This predicts that the Moses illusion should be less likely to occur in depressed mood states than in elevated mood states. It follows that bipolar patients, who display both extremes and can act as their own controls, should detect false presuppositions more readily when depressed than when manic. This prediction was confirmed in a longitudinal study using a task in which the pragmatic implications of a preceding statement were questioned. Patients in a depressed state were more likely to detect a false presupposition than when they were in a manic state. Patients' ability to attend to successive non-semantic targets (i.e. digits), as indexed by the SART (Robertso, Manly, Andrade, Baddeley, & Yiend, 1997), showed comparable decrements in both states (Barnard, Palmer & Scott, & Knightley, submitted). Hence, a simple explanation based on general attentional mechanisms being more widely disrupted in mania than in depression could be ruled out, and our effect linked to the preferential adoption of different modes of processing meaning.

CE3.2.2 Executive modes and schematic models in anxious states.

The ICS analysis of alternative modes applied in processing two levels of meaning offers a novel theoretical perspective on the processing of threat-related material by people in anxious states. Monitoring for threat related material could plausibly rely on the mechanism taking brief glances at implicational meaning, while the engagement of attention with threatening material could involve taking a more extended look at propositional meanings. Task-related and individual difference variables should both influence a generic salience parameter controlling mode shifts. We investigated this possibility in a series of three studies using the attentional blink paradigm in which we introduced threat-related distractors.

We first showed that physical threat words, unrelated in meaning to the target category, were capable of capturing attention in the AB paradigm, but only for trait anxious individuals who were state anxious at the time. Furthermore, the serial position curves indicated that the blink for threat material occurred later, and was briefer in duration, than that obtained previously for distractors more highly related in meaning to the targets. This suggested that attention under these circumstances was captured but not followed by a detailed look of the kind that occurred in our earlier experiment with healthy volunteers (CE3.1.2). A second experiment showed that social threat words had only minimal effects, like those of a simple category change in our earlier experiments. The respective contributions of semantic similarity and threat-relatedness were then examined in a more sophisticated design that used Latent Semantic Analysis to index both threat-relatedness and semantic similarity. In a context where jobs/occupations are the targets, distractors like villain and miser both have high levels of semantic association to the target category, but differ in their threat associations. Words like seducer and vegetarian show low levels of semantic associations to targets, but again differ in threat associations. The results replicated the basic effects of both semantic similarity (see 3.1.2) and of threat. All these words capture attention significantly to a greater or lesser extent, but the time to taken to engage a detailed propositional evaluation of a distractor's meaning, the depth and duration of that evaluation, vary with indices of state and trait anxiety. Anxious individuals do not just show a deeper blink to threat. Rather, the way they pay attention to meaning follows different patterns over time. These studies showed that an adequate theory of executive aspects of attention to affect-related meaning will require detailed modelling of task-induced salience, personal salience attributable to alternative self-models, and parameters determined by current affective state (see CE3.3.1 below).

CE3.3 Depression, self-models & memory

In the ICS architecture, representations are preserved in both the short and long term in memory records linked to specific subsystems. Recall and recollection are intimately bound up with attention to different levels of meaning or form (Barnard, 1999). Properties of encoding and retrieval in depressed states are theoretically related to both modes of executive control and schematic models (Teasdale & Barnard, 1993). In the current reporting period, we have investigated relationships between executive mode and schematic models in depression.

CE3.3.1 Autobiographical recall in depressed adolescents

Working in collaboration with Park (Dept. of Psychiatry Cambridge), we investigated autobiographical memory in adolescents with major depression. Independent groups in episode or in remission were given a series of autobiographical prompts. Case grammar analysis, based on linguistic distinctions concerning the generic semantic roles assigned to human agents, was used to analyse the verbal protocols. We found that self-reference in natural discourse differed between individuals currently depressed and those in remission. Currently depressed adolescents made proportionately fewer references to self-as-agent in an event, more state-based references to self and self-experience, and they also exhibited heightened used of negation, when compared to those with a diagnosis but not currently depressed. This supports the hypothesis (Teasdale & Barnard, 1993) that the model in place changes on generic features, such as agency, when depression remits. Reference to self-as-agent was negatively correlated not only with depressed state but also with an index of ruminative response style. Hence this result extends previous research by demonstrating an effect using an implicit measure of self-modelling expressed in natural discourse, as opposed to those based on questionnaires. When compared to a matched non-clinical sample, both the depressed and remitted groups gave reliably more propositions that referenced content beyond the context cued, an index of non-specific, or overgeneral recollection within this paradigm. This result effectively confirms previous findings obtained with the standard Galton cuing paradigm but using a new measure. The amount of overgeneral, or non-context specific material produced did not correlate with measures of current state or rumination (Barnard, Park & Ramponi, in preparation). Whereas the standard Galton procedure simply differentiates specific and overgeneral memories, our more refined methodology suggests that some attributes of the schematic models in place vary with current state. However, the attributes that change do not appear to be those that lead to overgeneral memories, which implies that other attributes do not vary with current state. Plausible determinants of this contrast were pursued in the next study which examined recollection in both autobiographical and recognition memory for word lists.

CE3.3.2 Recollection, self-models, modes and dysphoric mood

Using non-clinical samples of dysphoric and non-dysphoric participants, we investigated whether or not autobiographical recollection and non-autobiographical recollection for word lists were governed by the same determinants. Interest was focused on an assessment of the contributions of two factors. A predisposition to use a propositional mode of executive control was indexed by a ruminative response style. This was predicted to be associated with the production of fewer specific autobiographical memories and poorer recollection of list items. Self-complexity has been hypothesised as a vulnerability factor for depression (Linville, 1987). Those with more complex schematic models are argued to be less vulnerable. In a previous reporting period we had shown that those with more complex descriptions of daily routines showed greater recollection of specific autobiographical events (Eldridge, Barnard & Bekerian, 1994). We therefore hypothesised a general relationship between the complexity of self-models and recollection. Those with more complex models should be able to elaborate processing of both autobiographical and non-autobiographical material, and hence show enhanced recollection. The effects of this variable should be independent of the mode of executive processing. The complexity of self-and other-models was assessed using the Levels of Emotional Awareness Scale (Lane, Quinlan, Schwartz, Walker, & Zeitlin., 1990). Autobiographical recollection was assessed using the standard Galton cueing technique, while recollection of emotional neutral word lists was assessed in the remember-know paradigm (e.g. Gardiner & Richardson-Klavehn, 2000). The same samples of volunteers were assessed on both tasks. The dysphoric group showed a substantial deficit in recollection of list items and also recalled fewer specific autobiographical memories. The two measures were related: those recalling fewer specific autobiographical memories also recollected fewer list items. In both tasks multiple regression showed that unelaborated schematic models and a ruminative response style independently predicted a substantial proportion of the variance in recollection, with dysphoria contributing little. From this we conclude that the properties of schematic models and modes of executive control are the principal determinants of impaired recollection across tasks, rather than depressed mood per se (Ramponi,& Barnard, submitted). Such an analysis provides a more precise foundation for developing computationally explicit models than those theories that simply attribute memory impairments to a deficit in controlled rather than automatic processing.

CE3.4 Addressing the challenge of modelling highly concurrent architectures

The development of computationally explicit models is particularly challenging in the domain of cognition and affect. Multilevel theories emphasise highly concurrent processing both within local networks and on the wider scale of multiple interacting subsystems. In the current reporting period three avenues of modelling research have been pursued.

CE3.4.1 Analysis and simulation of multi-component, concurrent architectures

For modelling interactions among multiple subsystems our approach has been to explore and develop concepts for systems analysis (Barnard, May, Duke, & Duce, 2000, 2001). We proposed four particular concepts to organise more refined analyses of the behaviour of complex information processing systems: the configuration of information processing resources, their capabilities, the requirements that must be met for those capabilities to work, and the mechanisms that control and co-ordinate resource use. These concepts support the development of methods, and notations for analysing the resource requirements of particular mental tasks (Barnard & May, 2000; May & Barnard, in press). They also provide the foundation for developing computationally explicit models of highly concurrent architectures where resources can be rapidly re-configured in real time.

In one form of modelling, production system techniques were reported that automate ICS-based theoretical reasoning (Barnard & May, 1999). A second approach used an augmented form of modal action logic to demonstrate how mathematics can give rise to formal proofs of the application of ICS in behavioural tasks requiring complex actions and the integration of multi-modal sources of information (Duke, Barnard, Duce, & May, 1998). In a third approach, we have used process algebra to develop a running computational model of the attentional blink phenomena (Bowman & Barnard, 2001; Barnard & Bowman, submitted). This implemented attention switching between two levels of meaning. It relied on the idea of monitoring salience by glancing at incoming implicational representations and then switching to a more detailed look at propositional meaning only for those items found to be salient. Our use of process algebra simulates mental operations at a level of abstraction rather higher than that afforded either by traditional connectionist or symbolic methods. It operates at a level of process exchange and control directly analogous to the box models of cognitive psychology. We believe that this novel modelling technique, and our specific model of the attentional blink, have both broken substantial new ground. By actively researching alternative modelling methods our commitment is to find the best way of modelling the behaviour of interacting subsystems, rather than focussing all our efforts around one modelling technology, such as symbolic, connectionist, or hybrid methods.

CE3.4.2 Relating the modelling of cognitive systems to the modelling of neural systems.

In parallel with the other strands of modelling research one of our PhD students (Battye) has developed a connectionist model of the emotional Stroop effect (Battye, Barnard and Page, submitted). This work identified problems with a prior connectionist model of the emotional Stroop (Matthews and Harley, 1996) and rectified them. One key insight obtained from this new model was that apparently conflicting psychological theories of the emotional Stroop effect can all be traced back to the activation of common pathways in an underlying connectionist model. Battye has also developed a connectionist model of the attentional blink effect that offers the prospect of accounting for related cognitive phenomena on the basis of common underlying mechanisms, and relating those mechanisms to candidate brain systems such as the anterior cingulate cortex (Battye &

Barnard, 2002). Another graduate student (Tavares) is currently using animated vignettes to determine how schematic models that differ on affect related dimensions, such as affiliation or antagonism, differentially activate frontal and posterior brain regions.

The Barnard and Bowman (submitted) process algebra-based model of the attentional blink implemented two modes of processing meaning with a delay line mechanism for holding active representations. Delay lines, which are essentially a linear arrangement of circuits which pass information states "down the line," have already been proposed as plausible functional correlates for the network structures observed in, for example, cerebellar cortex (Abeles, 1991) and could equally well exist in other cortical areas. In the current reporting period we have completed an initial phase of research (Barnard, report in private circulation) that has worked out how a subsystem of cognitive processes, like those proposed in ICS, could emerge from interactions among neural delay lines. Oscillations in the build up of delay line content offer one means for predicting when evoked electrical potentials should occur in response to changes in salience parameters in tasks such as the attentional blink. The qualitative nature and number of delay lines needed to represent a principal components analysis of the material being processed can also form a basis for predicting patterns of brain activation. This particular outcome of the theoretical work in the current programme forms a key component of our future proposals summarised later under Emotion programme E3.

Project CE4: Interactions of "automatic" affective and "controlled" cognitive processing in the maintenance of affect.

Scientific Direction: Dalgleish (15%), Mathews (35%).

Grant-supported scientists: Ridgeway (2 years, 100%).

Research support: Yiend, (35%).

MRC-supported students: Rafter, (3 years, 100%), Wood (3 years, 100%), Yiend (3 years, 100%).

CE4.1 Attentional bias and anxiety

Individuals vulnerable to anxiety are more attentive to threatening cues than are less anxious individuals (see Mathews & MacLeod, 1994). The methods used in previous studies have not enabled a distinction to be made between attentional engagement (a process in which attention is initially captured by stimuli) and attentional disengagement (in which attention is removed from one object or location and allocated elsewhere). Engagement and disengagement may involve different brain systems, and establishing which is most involved in differential attention to threatening cues could have implications for modifying vulnerability to anxiety (see Project CE7).

Yiend & Mathews (2001a) investigated this issue using a method developed by Posner, in which a single emotionally neutral cue stimulus indicates the location of a target that follows. These so-called valid trials lead to faster detection of the target, while occasional invalid trials (in which the target appears in an alternative location) lead to slowing due to having to relocate attention. When the cues were pictures having threatening or neutral content, anxiety-prone individuals were particularly slow relative to controls in the invalid trials, but only when the pictures were threatening. The distinction between anxiety-prone groups was present when cues were displayed for 500ms but was reduced after 2 seconds. It was concluded that the attentional bias in anxiety involves a difficulty in disengaging attention from threatening cues at early stages of processing.

In a further series Mathews, Fox, Yiend & Calder (submitted) showed that this extends to locations having threat connotations. Faces with neutral or fearful expressions were displayed centrally, with eyes gazing to the right, left, or straight ahead. Target letters appearing randomly to the left or right, were detected more slowly when gaze had been directed to the other location than in the direction of gaze. In highly anxious individuals, target detection was particularly speeded in valid trials, when targets appeared in the direction indicated by a fearful (rather than neutral) gaze, and was particularly slowed in corresponding invalid trials. There was no such distinction due to fearful expression in low anxious individuals. It can be concluded that attending to the direction of another person's gaze is relatively automatic, and that the attention of anxiety-prone (but not low anxious) individuals is more strongly guided by eye gaze when a fearful expression implies the presence of danger. This evidence supports further the view that the attentional processing biases associated with vulnerability to anxiety will increase awareness of potential dangers, and thus may serve to maintain anxious mood (see also CE7).

CE4.2 Attention to threat in patients with life-threatening disease

Work on the prediction of anxiety in breast cancer patients (supported by a grant from the CRC to Mathews) has now been completed. A number of measures obtained immediately prior to diagnosis, including a measure of attention to emotional words, were predictive of distress four months later. These results show that patients who are prone to anxiety and health worry prior to diagnosis will continue to experience relatively greater emotional problems on follow up (Mathews, Ridgeway, Warren & Britton, 2002). These data have implications for predicting which patients may profit from anticipatory counselling following diagnosis of cancer.

CE4.3 Interpretation of emotional ambiguity

With Hirsch at the Institute of Psychiatry (London) Mathews has investigated the extent to which social phobia is associated with "on-line" interpretation of ambiguously threatening social events. Based on earlier work (Hirsch & Mathews, 1997), it was supposed that people without severe social anxiety typically attend to external cues (e.g. others' reactions), and tend to make positive inferences about their own social performance. In contrast, socially phobic individuals appear not to make such on-line inferences, either positive or negative, perhaps because their processing resources are depleted by anxiety and/or diverted to internal cues. Nonetheless, social phobics judge their own social performance harshly, presumably based on their prior expectations and internal feelings rather than external information.

To test this hypothesis, social phobic patients and non-anxious controls were asked to read descriptions of ambiguously threatening social events (interviews) while imagining themselves in those situations (as the interviewee). At unpredictable points in the text they made speeded lexical decisions for words that matched either a possible positive or a negative inference. Relative to an unambiguous control condition, at ambiguous points in the text non-anxious individuals were slower to endorse negative (but not positive) words matching possible inferences. Social phobics were always slower at ambiguous points than when the text was unambiguous. These data are consistent with the view that normal positive inferences are blocked in social phobia, and that this may contribute to the persistence of anxiety even in benign situations (Hirsch & Mathews, 2000).

One reason that social phobics fail to make positive inferences is that they report being distracted by negative images of themselves in social situations. When trained to replace these negative images with more benign versions, social phobics' anxiety decreased, and this improvement was apparent to blind observers of their social performance (Hirsch, Clark, Mathews & Williams, in press). Furthermore, when non-phobic volunteers were trained to hold negative self-images of themselves in mind, they came to resemble social phobics in failing to make normal positive inferences about social situations. It thus appears that an internal focus of attention on negative images both enhances anxiety and blocks protective positive inferences in social phobia.

CE4.4 Inhibitory processes and emotion

Mathews has explored negative priming of emotional and non-emotional words as a possible index of the ability to suppress responses to previously attended emotional words. Such failures of inhibition have previously found to be characteristic of Obsessional Disorders. Negative priming refers to the finding that when two items are presented with only one to be selected for report, it takes longer to name an item that was ignored in the preceding trial. Theoretical accounts of this phenomenon suggest that prior ignoring of the later to-be-selected item is crucial. In a novel procedure originally developed by MacDonald, Joordens, & Seergobin (1999), two words are presented together for a comparative judgement (e.g. which animal is larger?). In the critical trials, the non-selected item in a preceding trial becomes the to-be-selected item in the current trial. MacDonald et al. claimed that prior attention to the non-selected item did not prevent negative priming, but actually enhanced it. Mathews, Mackintosh & Holden (in press) found that, to the contrary, correct matching of ignored repetition and control item content revealed no negative priming at all if the to-be-selected items were previously attended and then rejected. Earlier conclusions from studies using this method, suggesting that Obsessive Compulsive patients show large negative priming effects (implying intact inhibitory processes) are thus invalid.

Mathews and Dalgleish (Wood, Mathews & Dalgleish, 2001) used a different technique to investigate the prediction that emotionally vulnerable individuals have particular difficulty in the inhibition of emotional processing. In a series of experiments, a reading task was performed that required the suppression of emotional or neutral meanings. Participants read sentences, some of which ended in threat/neutral homographs (e.g. Some puddings are made using batter) and were then required to decide if another word was related to the meaning of the sentence (e.g. injury). In these critical sentences, the threatening meaning was irrelevant and so must be rejected. Decisions involving homographs were significantly slowed relative to control sentences. When threatening (rather than neutral) meanings had to be suppressed, anxious participants made more errors and were also sometimes slower than control groups. It was concluded that inhibition of threat meanings may be more difficult in anxiety-prone individuals, consistent with the difficulty they experience in disengaging attention from threatening locations (see also Yiend & Mathews, 2000a).

This difficulty in inhibiting congruent emotional material in individuals prone to emotional problems was further investigated by Dalgleish and collaborators in patients with clinical depression using a directed forgetting (DF) methodology (Power, Dalgleish & Claudio, 2000). The DF paradigm requires individuals to try to forget information that they had previously been instructed to remember. The DF literature shows that successful forgetting in this context involves direct inhibition of the to-be-forgotten material. In this series of studies depressed and control participants were instructed to forget emotional and neutral material. DF was measured relative to a (remember) control condition in which no instruction to forget was given. The data showed that the depressed patients, but not the controls, showed no DF effect for emotional words. This provides further evidence of a difficulty in inhibiting emotional information in vulnerable and clinical groups.

Dalgleish and Mathews (Dalgleish, Mathews & Wood, 1999) outlined a theoretical framework for conceptualising inhibitory processes in cognition-emotion relations that rested on the distinction between automatic and controlled cognitive processing. A two-by-two taxonomy of inhibitory processes was outlined involving automatic and controlled processing of emotional cognitive content and automatic and controlled processing of emotional feelings and behaviours. Dalgleish (in collaboration with Andrews at the University of Essex) investigated this controlled/automatic distinction in a large sample of emergency service workers who were asked to respond to test items describing different putative ways in which they inhibited aspects of affect in relation to a specified traumatic event. Two clear factors emerged reflecting controlled (e.g. Do you make an effort to not talk about what happened?) and automatic (When you go over the event do your emotions feel numb?) inhibition processes. These factors significantly predicted levels of post-traumatic stress in a longitudinal study of a subset of the original sample. The factor structure was confirmed in an additional study of patients with eating disorders who had experienced traumatic life events (Andrews, Joseph, Troop Van Rooyen & Dalgleish, submitted).

Project CE5: Multi-level analyses of emotional disorders

Scientific Direction: Barnard (10%), Dalgleish (60%), Teasdale (20%).

Research support: Golden (80%), Green (10%), Ramponi (10%).

MRC-supported students: Dunn (3 years, 100%).

Grant-supported students: Sheppard (3 yrs,100%), Du Toit (2 yrs, 100%), Bishop (3 yrs, 20%).

Unique features of the work of the Cognition and Emotion group include: (1) integration of basic research on the interaction of cognition and emotion; (2) the development of comprehensive, multi-level, information processing theoretical frameworks on the basis of that research; (3) the development and investigation of analyses of specific emotional disorders within those frameworks; and (4) application of these analyses to understanding and developing psychological treatments for emotional disorders. Work in Project CE5 in the report period has taken forward step 3, multi-level analyses of emotional disorders, in two new directions: (a) inclusion of a developmental perspective; and (b) applications to new disorders.

CE5.1 Developmental aspects of emotional disorder

Multi-level analyses of emotional disorder in adults (e.g. Mathews & Mackintosh, 1998; Power & Dalgleish, 1997; Teasdale & Barnard, 1993) focus on the way that self-perpetuating patterns of information processing, frequently including mood-related cognitive biases, contribute to the onset and maintenance of disorder. For example, increased accessibility of self-devaluative material in depressed mood in individuals vulnerable to major depression is assumed to contribute to the maintenance and escalation of those moods; attentional biases to threat in anxious individuals are assumed to contribute to the development of generalised anxiety disorder. It is assumed that these self-perpetuating patterns are learned, but there has been very little research investigating the cognitive processing of emotional information in child and adolescent emotional disorders to determine when, developmentally, these patterns are established (Vasey, Dalgleish & Silverman, in press). Such research is important because in other areas of developmental psychology, there is evidence that cognitive processing follows a clear developmental course and is markedly different in younger groups relative to adults across a number of paradigms and cognitive domains.

CE5.1.1. Cognitive biases in childhood and adolescent emotional disorders

Dalgleish, with colleagues at the Institute of Psychiatry, carried out a large set of studies to address the following questions: 1) Do processing biases for emotional information exist in younger populations with emotional disorders? 2) If so, to what extent are they similar to such biases in adult samples? 3) What is the developmental course of such processing biases? The research involved 3 clinical samples of children and adolescents with diagnoses of Major Depressive Disorder (MDD), Generalized Anxiety Disorder (GAD), and Posttraumatic Stress Disorder (PTSD). The cognitive tasks were similar to those used with adult disorders and included measures of attention (the dot probe paradigm and the modified Stroop task), recognition and recall memory (for emotional words and trait adjectives), prospective cognition (probability estimates for future negative events), and the interpretation of ambiguity (homograph interpretation).

The most striking finding of these studies was that childhood and adolescent emotional disorders were each characterised by particular biases in processing emotional information that were very similar to the biases shown in corresponding adult disorders, and different from the pattern of biases shown in other disorders (Dalgleish et al., in press). The GAD and PTSD groups exhibited clear attentional and interpretative biases for threat-related material: (Dalgleish, Moradi, Taghavi, Neshat-Doost & Yule, 2001; Moradi, Taghavi, Neshat-Doost, Yule & Dalgleish, 1999a; Taghavi, Dalgleish, Moradi, Neshat-Doost & Yule, in press; Taghavi, Moradi, Neshat-Doost, Yule & Dalgleish, 2000; and Taghavi, Neshat-Doost, Moradi, Yule & Dalgleish, 1999). In contrast, attentional effects were absent in the MDD sample (Neshat-Doost, Moradi, Taghavi, Yule & Dalgleish, 2000; Neshat-Doost, Taghavi, Moradi, Yule & Dalgleish, 1997). Conversely, MDD children and adolescents, and a sub-clinically depressed sample, exhibited memory biases for negative self-encoded material (Neshat-Doost, Taghavi, Moradi, Yule & Dalgleish, 1998; Bishop, Dalgleish & Yule, submitted), but such biases were not shown by the GAD and PTSD children. The broad similarities between the cognitive biases shown by adult and childhood presentations of individual emotional disorders suggest that the disorder-related self-perpetuating processing patterns to which these biases contribute can become established relatively early in development. The main difference between the findings observed by Dalgleish and colleagues and previously reported findings in adults was that, on the prospective cognition measure, GAD, MDD and PTSD children, unlike their adult counterparts, showed no tendency to estimate negative events as more likely to happen to themselves than to others (Dalgleish, Moradi et al., 2000; Dalgleish, Taghavi et al., 1997). Follow-up studies suggested that the lack of a negative self-referent bias in clinically distressed children and adolescents reflected the operation of strategic inhibition mechanisms that served to protect the young patients from distressing material (Bishop, Dalgleish, Nimmo-Smith & Yule, submitted; Dalgleish et al., 1998; Dalgleish, Wood & Yule, submitted).

The developmental course of the different forms of processing bias in younger clinical groups was investigated using regression techniques. These showed that, within the age range studied (8 to 18), there was no evidence for a developmental progression in the measures of attentional bias, suggesting that these biases are established early and are relatively constant subsequently. In contrast, the strength of the relationship between depressed mood and memory bias in the MDD sample increased significantly with age. This finding is consistent with the hypothesis that such processing is underpinned by negative schematic self-representations. Other developmental evidence would lead us to expect that such representations would become more elaborate over development in ways that would increase self-referent memory biases.

CE5.1.2 Overgeneral autobiographical memory in major depression

In overgeneral autobiographical memory (OGM) individuals, asked to recall memories of specific events, produce, instead, categoric descriptions summarising repeated instances of such events. OGM occurs in major depression, predicts the course of this disorder, has been linked with cognitive avoidance and rumination (CE7), and is assumed to reflect core aspects of depressive psychopathology. All previous studies of OGM have been in adults. Teasdale, in collaboration with Park and Goodyer (Park, Goodyer & Teasdale, 2002) has demonstrated, for the first time, OGM in first episode major depression in adolescents. This finding is important in demonstrating that OGM is not an aftereffect of previous episodes of depression, and that it characterises developmentally early forms of major depressive disorder just as much as adult forms.

The tendency to generate overgeneral autobiographical memories has been associated with reports of childhood abuse in depressed patients (Kuyken & Brewin, 1995). In order to disentangle the relationships of depression and early trauma to OGM, Dalgleish, Tchanturia et al. (submitted) examined OGM in a group of patients with eating disorders for whom the primary diagnosis was not depression, but who, nonetheless, reported moderately high levels of both childhood abuse and depression. These patients generated more OGMs than controls, and the degree of OGM was positively associated with levels of self-reported abuse, even when levels of current depression were controlled for. These data, along with those of Kuyken and Brewin (1995) indicate that perceived early trauma, as well as significant levels of depression, are important contributors to OGM.

CE5.1.3 Cognitive vulnerability to first episode major depression in children and adolescents

Teasdale's (1988) differential activation hypothesis suggests that vulnerability to major depression is related to the kind of negative thinking patterns activated in states of mild depressed mood, rather than to the more trait-like aspects of thinking style emphasised by previous hypotheses. Activation of such patterns by current depressed mood is assumed to reflect a history of association between negative thinking and depressed mood in the past. This hypothesis can account for the observed progressive increase in risk for further episodes of depression with every consecutive episode experienced; each such episode provides further opportunities for associations to be formed between depressed mood and negative thinking. Studies in adults consistently support the differential activation hypothesis: recovered depressed patients (known to be at high risk for depression) show more negative depressogenic thinking than controls when assessed in induced or natural depressed mood, but not in non-depressed mood. It is not possible to tell from such studies whether the tendency for depressogenic thinking to be activated in dysphoria also preceded patients' first episode of major depression, constituting a prior vulnerability, or whether it was primarily a consequence or "scar" of earlier episodes. To address this issue, in work with Goodyer and colleagues (Kelvin, Goodyer, Teasdale & Brechin, 1999), Teasdale examined the thinking patterns of high emotionality children, known to be at risk for depression, who had not yet experienced an episode of major depression. As in adults, in induced depressed mood, high risk children showed more globally negative self-referent thinking than low risk children, but the groups did not differ in neutral mood. These findings demonstrate, for the first time, that the tendency to switch in depressogenic thinking in dysphoria constitutes a prior vulnerability for major depression.

CE5.1.4 Everyday memory in children and adolescents with PTSD

Research in adults with PTSD has shown that they present with impaired memory functioning (e.g. Yehuda et al., 1995) on a range of neuropsychological tasks. However, no such research has been carried out on younger populations. This is important because children and adolescents with PTSD are normatively pursuing their education and any impairments in memory, however short-lived, could have profound long-term consequences. Dalgleish and collaborators therefore examined memory functioning in children and adolescents with PTSD using the Rivermead Behavioural Memory Test, a set of tasks that taps everyday memory processes (Moradi, Neshat-Doost, Taghavi, Yule & Dalgleish, 1999b). Overall, the PTSD youth showed poorer memory performance than the controls. In particular, they were worse on tests of prospective memory where they had to remember an intention to carry out an act. These data suggest that attention needs to be paid to everyday cognitive functioning in young trauma survivors.

CE5.2 Applications to new disorders

CE5.2.1 Seasonal depression

In Major Depressive Disorder with Seasonal Pattern (MDD-SP), or seasonal depression, patients are in episode in the winter and in remission/recovery in the summer. Because variation in this disorder is so closely linked to biologically relevant seasonal rhythms, it is often assumed that these variations may be more directly biologically determined than in more common forms of unipolar depression. For this reason, Dalgleish used the study of seasonal depression as an opportunity to examine the generalisability of previous findings in unipolar depression to a condition that was clearly related, but that might have a different aetiology.

Dalgleish, Spinks, Kuyken and Yiend, (2001) found that, unlike patients with typical major depression, seasonally depressed patients did not differ overall from healthy controls on overgeneral autobiographical memory (OGM) when the 2 groups were compared in the winter, when the seasonally depressed patients were symptomatic. This lack of a significant cross-sectional OGM effect in seasonal depression was surprising given that the performance of seasonally depressed patients on other cognitive measures such as attributional style (Levitan et al., 1998) is similar to that in non-seasonal depression. Further, winter OGM scores, although not significantly elevated in the seasonally depressed, did predict the extent to which these patients recovered on observer-rated symptoms of depression the following summer. It was hypothesised that seasonal depression is not associated with fundamental shifts in elaborative cognitive processing, as indexed by explicit memory tasks, while nevertheless being associated with negative biases on tasks with a large self-report/response bias component, such as questionnaire measures. This idea was examined in a follow-up study (Dalgleish, Spinks, Golden & Du Toit, submitted) in which performance on a different memory measure - recall memory for trait adjectives - and on a self-report measure - the attributional style questionnaire (ASQ) - were assessed in healthy controls and a group of seasonally depressed patients in the winter when they were symptomatic. Again, patients were followed up in the summer and symptoms of depression were assessed by interview. The MDD-SP group differed from controls on the ASQ (in the predicted depressogenic way) but not on the recall measure. However, as with OGM, recall of self-referent negative adjectives predicted later symptom outcome. These studies suggest (a) that aspects of the mnemonic processing of emotional information in seasonal depression play an important role in the maintenance and recovery from the disorder but (b) that seasonal depression seems to differ from non-seasonal depression in that it is not associated with overall biases in memory for emotional information, as measured by both autobiographical recall and recall of trait adjectives. This may be because the aetiology of seasonal depression is more closely associated with biological factors than with cognitive ones (Dalgleish, Rosen & Marks, 1996).

CE5.2.2 Four sources of variation in dysfunctional ideation and affective states

ICS has previously been applied to the analysis of unipolar major depression (Teasdale & Barnard, 1993; and see CE7 and CE8). Barnard (in press) has extended the ICS analysis of symptom expression to a wider range of cognitive-affective psychopathology. He identified four theoretical sources of variation in the processing of propositional and implicational levels of meaning: Self-models, modes, how they are switched as a function of control parameters (e.g. salience, rate of change), and the consequences of asynchronous exchanges between subsystems. The schizophrenic spectrum of symptoms was related to the consequences of asynchronous exchanges between two levels of meaning. The symptoms of mania were related to high rates of change in implicational representations and to a predominance of experiential buffering at this level of representation, rather than the analytic buffering of propositional representations linked to depressive states. This illustrated how different, yet overlapping constellations of symptoms can arise when specific properties of executive processing move outside their normal range of operation. Some of the evidence leading to or predicted by this analysis was summarised in section CE3.

CE5.2.3 Theoretical modelling of PTSD

Dalgleish (submitted-a) has reviewed the major cognitive theories of PTSD and argued that they represent a paradigm case for the evolution of theorizing in psychopathology from single 'level' associative network or mental schema models of disorder to the types of multi-representational architectures that have been developed in the Cognition & Emotion group - SPAARS (Power & Dalgleish, 1997) and ICS (Teasdale & Barnard, 1993). This paper argues that three core representational systems (schemas, propositional representations, and associative representations) are necessary to provide comprehensive accounts of a range of psychopathology, using PTSD as the paradigm case. However, the cognitive theories of PTSD are called to account for their underspecification of the mechanics of theorising, for example how information is transferred from one type of representation to another, and this is targeted as a major item on the theoretical agenda.

CE5.2.4 Counterfactual reasoning in trauma survivors

A key feature of the clinical presentation of trauma survivors is the experience of intrusive and distressing thoughts about the original traumatic event. Often these thoughts are of a counterfactual (CF) nature whereby individuals try to imagine how the event might have turned out differently if a significant aspect had been different - mental undoing (Dunmore, Clark & Ehlers, 1999). Events can be mutated or undone in an upward direction to provide a better outcome (e.g. "if only I had not gone out that day then the accident would not have happened") or in a downward direction to provide a worse outcome. Mutations can be about self-related or other-related behaviours. Upwardly mutating the event has negative affective consequences as the individual is presented with an imagined way in which the trauma could have been avoided or ameliorated. Despite this emotional cost associated with upward mutations, clinical anecdotal evidence suggests that these are the most common form of CF intrusion in Posttraumatic Stress Disorder (PTSD).

Dalgleish (submitted-b) investigated this issue empirically in trauma survivors with and without PTSD to determine whether upward CFs were indeed normative in the disorder and, if this was the case, to examine what the function of such CFs might be. The first study revealed that trauma survivors did invariably make upward, self-referent CFs about their trauma, even though they had minimal control over the unfolding of the traumatic event at the time. However, the second study showed that this pattern was the same regardless of PTSD status. It was hypothesised that this pattern of CF reasoning might reflect attempts by all trauma survivors to integrate an element of self-control into their representation of the trauma by hypothetically mutating aspects of their behaviour such that the trauma could have been prevented. This cognitive gain might outweigh the negative affective cost of such CFs. A third study investigated whether this CF style transferred to events other than the original trauma and whether it varied with the objective controllability of the event. Trauma survivors and never-traumatised controls generated CFs to high- (car crash) and low-controllability (hurricane) accident scenarios. The results revealed that trauma survivors generated self-referent CFs to both high- and low-controllability scenarios. This was again independent of PTSD status. In contrast, controls showed this pattern for high controllability events, but not for low-controllability events, where the CFs were more likely to be other-referent.

It remained possible that this prevalent, self-referent CF style in trauma survivors was a function of priming of the original trauma memory by the research recruitment process which emphasised the psychological processing of trauma. In order to examine this possibility, a final study involved priming healthy volunteers to reflect on either a neutral life event or a negative, uncontrollable life event, prior to carrying out the scenario task described above. The results revealed that priming with a negative event did not induce a more self-referent CF style. Indeed, it had the opposite effect, indicating that such priming is unlikely to be a significant factor in the pattern of results in the trauma survivors. This set of studies indicates that the experience of a traumatic life event, regardless of whether or not that event leads the victim to develop PTSD, seems to result in a CF reasoning style that emphasises the upward mutation of self-referent behaviour, even for non-autobiographical events where changes in the person's behaviour could not reasonably have made any difference at the time. This is consistent with upward, self-referent CF reasoning having the cognitive function of reinforcing a sense of self-control following the experience of trauma

Project CE6: Neuropsychological deficits in recognition, perception and experience of emotion

Scientific Direction: Calder (40%), Dalgleish (25%), Lawrence (30%).

Research support: Golden (20%), Keane (40%).

MRC-supported students: Croucher (1 yr, 100%).

Project CE2 addressed the perceptual processing (i.e., front-end encoding, configural processing, etc.) of facial expressions. A full understanding of facial expression recognition requires an appreciation of the mechanisms underlying the identification of the emotions displayed (i.e., that a facial expression signals fear, rather than anger or disgust, etc.). Calder has addressed this by studying different patient populations. In earlier research, Calder and collaborators found initial evidence that the recognition of facial signals of fear and disgust may be supported by separate neural systems (Calder, Young, Rowland, Perrett, Hodges, et al, 1996b; Sprengelmeyer, Young, Calder, Karnat, Lange, et al, 1996). Bilateral amygdala lesions were found to impact primarily on the recognition of fear, and to a lesser extent anger, (Calder et al., 1996b) whereas patients with Huntington's disease showed a disproportionate impairment in recognising facial expressions of disgust (Sprengelmeyer et al., 1996). Project CE6 has built on these findings, characterising more completely the functional and neurological dissociation between fear and disgust processing. In addition, work with Lawrence has addressed the neural underpinnings of anger processing. These findings have important theoretical implications and are reviewed in a recent Nature Reviews Neuroscience article by Calder, Lawrence, & Young (2001b). The research addresses a longstanding debate concerning whether the representation of emotion involves individual systems for separate emotions, or an integrated system for all emotions (Calder et al., 2001b). More specifically, the research provides insights into the neural mechanisms underlying the recognition of individual emotions, and highlights parallels between human and comparative research (LeDoux, 2000; Garcia, Forthman Quick, & White, 1983). On the basis of these findings we have proposed that an effective approach to the neuropsychology of human emotion is to use phylogenetic data to guide a search for dissociable emotional systems.

CE6.1 A cross-modal system for recognising fear

Calder's collaborative neuropsychological projects have confirmed the amygdala's role in processing facial expressions of emotion, and in particular fear (Adolphs et al., 1999; Broks et al., 1998). In collaboration with Scott (University College London), Calder has addressed the contribution of the amygdala to the recognition of emotion from vocal cues (Scott et al., 1997) in a case study of DR, a lady with selective bilateral amygdala damage who shows impaired recognition of fear and anger (Calder et al., 1996b) from the face. DR showed an identical pattern in the vocal domain, supporting the view that the amygdala contributes to the recognition of these emotions across different sensory modalities (Calder et al., 2001b). This proposal is also supported by collaborative functional imaging (fMRI) projects with Phillips, and Morris and Dolan, which showed enhanced amygdala signals for facial (Phillips et al., 1998; Phillips et al., 1997; Morris et al., 1998) and vocal (Phillips et al., 1998) signals of fear. These observations lend support to Calder et al.'s (2001b) proposal that fear recognition is achieved by a mechanism that codes emotional information from multiple sensory modalities.

CE6.2 A dissociation between fear recognition and memory for negatively-valenced material

Recent functional imaging and patient-based research has implicated the amygdala in enhanced memory for negatively-valenced material. In collaborative work (Papps, Calder, Young, & O'Carroll, in press), Calder has investigated memory for emotional material in DR (see CE6.1; Calder et al., 1996; Scott, et al., 1997). DR showed intact memory for negatively valenced pictures and words, providing the first evidence that memory and recognition of negative material rely on dissociable systems. These findings were attributed to the fact that DR's amygdala damage is incomplete.

CE6.3 Disgust recognition in OCD and Tourette's syndrome

Calder's collaborative work with Sprengelmeyer has demonstrated that Huntington's disease (an autosomal dominant neurogenetic disorder that, in its early stages, particularly affects the basal ganglia) causes disproportionate impairments in recognising facial expressions of disgust (Sprengelmeyer, 1997). To further investigate the role of the basal ganglia in disgust processing, Sprengelmeyer and Calder (Sprengelmeyer et al., 1997b) examined two psychiatric disorders associated with abnormal metabolic activity in this brain region, obsessive compulsive disorder (OCD) and Gilles de la Tourette syndrome (Braun et al., 1995; Rapoport, 1989; Rapoport & Fiske, 1998). The results showed that the OCD group and a sub-group of the Tourette's participants with co-morbid OCD symptoms showed a selective impairment in recognising disgust facial expressions. One interpretation is that these findings emphasise the role of the basal ganglia in recognising disgust. In addition, it was proposed that the presence of OCD symptoms in the patients' childhood years may have led to a weakened mapping between self-experienced emotion and the facial expressions of others.

CE6.4 Functional imaging studies of disgust processing

Huntington's disease, OCD and Tourette's syndrome are not characterised by focal neuropathology. Hence, although these patient-based studies point towards the probable involvement of the basal ganglia in disgust, the evidence is indirect. In this respect functional imaging research has been particularly informative. Using stimuli developed from program CE2, Calder's collaborative work with Phillips (Phillips et al., 1998; Phillips et al., 1997) has identified two areas involved in processing facial expressions of disgust - the insula and the basal ganglia. Insula involvement is particularly interesting given its role in gustatory function (Augustine, 1996; Small et al., 1999). Of equal relevance is research showing that lesions to the insula or pallidum of rats interfere with conditioned taste aversion (Dunn & Everitt, 1988; Hernadi, Zaradi, Faludi, & Lenard, 1997). Together these findings concur with the theory that disgust has developed from a more primitive system involved in distaste (Rozin & Fallon, 1987; Rozin, Lowery, & Ebert, 1994).

CE6.5 A cross-modal system for recognising disgust

While functional imaging of healthy participants identifies brain regions that are correlated with certain behavioural tasks, it provides no information about whether these regions are necessary and sufficient for successful performance of these tasks. Hence, it is important that Calder has provided further evidence for the role of the insula/basal ganglia regions in processing disgust in the form of a case study of a man (NK) with a focal lesion affecting these areas (Calder, Keane, Manes, Antoun, & Young, 2000b). NK's damage is lateralised to the left and includes the insula, putamen, internal capsule, globus pallidus, and the head of the caudate. NK showed highly selective impairments in recognising disgust from facial and vocal cues, and in his self-reported experience of this emotion. NK's results are consistent with damage to a system that is involved in the recognition of disgust from different modalities, and in the experience of disgust (Calder et al., 2001b).

CE6.6 Differential effects of ageing on the recognition of fear and disgust

In line with the proposal that separate neural systems underlie the recognition of fear and disgust, Calder and Manly have shown differential effects of ageing on the recognition of these emotions (Calder et al., in press). On two tests of facial expression recognition with five age groups ranging from 20 years to 70 years, increasing age produced a progressive reduction in the recognition of fear and, to a lesser extent, anger. In contrast, older participants showed absolutely no reduction in recognition of facial expressions of disgust; rather, there was evidence of an improvement. Recognition of other facial expressions showed no significant evidence of deterioration (or enhancement) across age groups. These results are consistent with the differential effects of ageing on two brain regions underlying the recognition of, respectively, fear and disgust. In relation to fear, research has shown that medial temporal pathology (including the amygdala) is a consequence of normal ageing (Anderton, 1997), while fMRI research has demonstrated reduced amygdala activation to negative facial expressions with increasing age (Iidaka et al., 2001). In contrast, the gross structure and neurochemistry of the pallidum, a region of the basal ganglia implicated in fMRI studies of disgust (Phillips, et al. 1997; Phillips, et al. 1998) and taste aversion (Hernadi et al., 1997), is largely spared by ageing (Raz, 2000).

CE6.7 The contribution of frontal systems to facial expression recognition

The work discussed above identified separate neural mechanisms involved in processing fear (amygdala) and disgust (insula and basal ganglia). Other studies have emphasised the important role of the frontal lobes in processing emotional cues in general, and some have suggested that the systems involved in coding individual emotions may feed into more general emotion systems in frontal cortex (Sprengelmeyer, Rausch, Eysel, & Przuntek, 1998). If this is correct, then we would expect to see general emotion recognition impairments following frontal cortex damage. Keane, Calder, Hodges and Young (2002) investigated this issue in a series of patients with frontal variant frontotemporal dementia (fvFTD), a condition that largely affects the frontal regions of the brain but particularly the ventromedial frontal lobes. Results showed that fvFTD was associated with impaired recognition of a number of emotions from both facial and auditory cues. In contrast, there was no evidence of impaired recognition of identity from faces. These results emphasise a role for the frontal lobes in processing emotional cues from different sensory modalities. In addition, they suggest that previous reports of impaired facial expression recognition in the absence of impaired facial identity recognition, may have been incorrect to interpret this pattern as the antithesis of prosopagnosia (impaired facial identity recognition). Rather, as suggested by the results of the fvFTD study, this pattern may instead reflect impaired recognition of emotion.

CE6.8 Perceptual and motor codes involved in facial expression recognition

It is tempting to think of the perceptual mechanisms underlying facial expression recognition as analogous to those for facial identity. However, we should be cautious in adopting this view because we not only recognise expressions in other people's faces, we generate them ourselves. Hence, the mental representation of facial expressions has the added requirement of a motor-program code (to describe how to produce the expression) in addition to a visual code. The extent to which these two codes interact is unclear. To investigate this issue, Calder studied a group of subjects with a rare congenital disorder that causes facial diplegia (Möbius Syndrome) (Calder, Keane, Cole, Campbell, & Young, 2000a), meaning that they have never produced normal facial expressions. Anecdotal reports had suggested that this group are severely impaired at recognising facial expressions, but until now, there has been no systematic research. Calder found no evidence of marked deficits in facial expression recognition in the Möbius individuals. These findings suggest that there may be minimal interaction between motor-code and visual representations for facial expression.

CE6.9 Selective deficits in anger recognition

Lawrence and Calder have used data from ethology and ethopharmacology to make and test predictions about selective deficits in emotion recognition. In particular, they argued that certain emotions (fear, disgust, anger) can be linked to processing in defense systems involved in detecting and coordinating flexible responses to different ecological threats. For example, appetitive aggression occurs in the context of resource/dominance disputes in a wide variety of species. Hence, the possibility arises that a specific neural system may have evolved to detect and coordinate responses to this specific form of challenge or threat. The dopamine system has been implicated in the processing of signals of aggression in social-agonistic encounters in several species. Acute administration of the dopamine D2-class receptor antagonist sulpiride was used to induce dopaminergic antagonism in healthy male volunteers. This produced a selective disruption in the recognition of facial expressions of anger (signals of appetitive aggression in humans), in the absence of impairment to other emotions (e.g. fear, disgust) or to facial identitiy processing (Lawrence, Calder, McGowan, & Grasby., 2002). These results provide strong support for evolutionary approaches to emotion, but are difficult to reconcile with approaches based on a limited number of dimensions, such as valence and arousal. Such approaches have difficulty explaining, for example, selective deficits in the processing of anger, but not fear.

CE6.10 Mechanism of psycho-surgery for depression

Patients who suffer from severe, chronic depression that is resistant to the standard interventions of pharmacotherapy and psychological therapy have the option of psychosurgery as a treatment-of-last-resort. Dalgleish and Teasdale, in collaboration with colleagues at the Institute of Psychiatry, investigated a group of patients who had undergone Stereotactic Subcaudate Tractotomy (SST) as anti-depressant neurosurgery. Typically SST leads to remission/recovery from depression in 60% of patients. However, it is unclear what the psychological mechanisms associated with this anti-depressant effect are, nor whether there are secondary cognitive/neuropsychological costs associated with the operation.

In order to address these two questions, patients who had recovered from depression following SST (SST-recovered) were compared to patients for whom the operation had not been successful (SST-depressed) on a broad range of cognitive and neuropsychological measures (Dalgleish, Yiend et al., submitted). The results revealed that the SST-recovered patients were insensitive to negative feedback information on a widely used decision making task (Bechara, Damasio, Damasio, & Anderson, 1994) relative to the SST-depressed group. However, there were no other differences between the groups on a broad neuropsychological test battery indexing language, general intelligence, attention, memory and executive functioning. The data were re-examined in a correlational analysis and it was also found that the degree of recovery from depression following SST, as indexed by depression self-report measures, was associated with increased insensitivity to negative information.

In order to investigate which group was performing normally, a sample of matched, never-depressed controls completed the task. The performance of the controls did not differ from that of the SST-depressed group but was significantly different to that of the SST-recovered sample, with the recovered sample showing greater insensitivity to negative feedback relative to the healthy, never-depressed individuals.

It remained possible that the performance of the SST-recovered patients was a function of recovery from depression per se rather than a function of recovery following psychosurgery. In order to examine this possibility, patients who had recovered from depression with medication alone (medication-recovered) also completed the task. Again the results revealed significantly augmented insensitivity to punishment in the SST-recovered group and the medication-recovered participants were no different to the healthy controls and SST-depressed samples.

This pattern of results suggests that SST for depression may work by inducing a relatively enhanced insensitivity to negative information. Such insensitivity would potentially disrupt the vicious cycles of processing of negative information that are seen as central to the maintenance of the disorder in the theoretical models developed in the Cognition and Emotion group (Power & Dalgleish, 1997; Teasdale & Barnard, 1993). The results also indicate that the anti-depressant effect generated by SST does not seem to be at the expense of a more general deficit in neuropsychological functioning as measured by a standard test battery. This is important clinical information for those who are contemplating this irreversible treatment-of-last-resort.

Project CE7: Attention and the manipulation of affect perpetuating processes

Scientific Direction: Mathews (45%), Teasdale (25%).

Research support: Green (75%), Yiend, (45%).

MRC-supported students: Hoppitt (I year, 100%), Potts (3 yrs, 100%).

The manipulation of cognitive processes assumed to produce or maintain emotional states and disorders provides an opportunity both to test multi-level analyses of those disorders, and to identify the key processes to be modified in clinical interventions to treat or prevent those disorders. Studies in both anxiety and depression have investigated the effect of attentional manipulations on affect perpetuating processes.

CE7.1 Threat-related biases

CE7.1.1 Manipulation of attentional bias

This project is concerned with the issue of whether emotional processing biases can be manipulated. Establishing such experimental control would allow us to investigate the mechanisms underlying individual differences in these processing operations, their causal relationship with emotional states, and consequently, whether and how this control can inform therapeutic applications. In a first series of experiments in the area, Mathews addressed specific hypotheses about the critical factors underlying individual differences in attention to mild threat cues such as words or pictures. One hypothesis is that these cues are more aversive for anxiety-prone individuals because they have experienced more unpleasant life events associated with them. A second is that, even if there are no such differences in association frequency, anxiety-prone people learn negative associations more readily. The third is that, even if threat cues are no more aversive for anxiety-prone individuals than for others, they are less able to prevent attention capture by these cues.

In a series of experiments, in collaboration with Mackintosh (and Fulcher), Mathews found evidence consistent with this last hypothesis (Fulcher, Mathews, Mackintosh, & Law, 2001). Neutral pictures were paired with neutral, positive or negative captions, while participants formed an image linking the two. After a delay, the negative-paired pictures were rated as less liked, with no differences between groups high or low in negative emotionality. However, in a task in which participants had to find targets superimposed on the pictures, the group with high negative emotionality were slowed by negative-paired pictures, while the low group was slowed more by positive paired pictures. These data suggest that, even when matched for emotional learning, new negative cues capture attentional resources more in those prone to negative emotions.

In a further study of this kind, Mackintosh & Mathews (in press) used a spatial cueing task to contrast attention to mildly emotionalised cues with that to more severely threatening pictures. In a non-anxious group there was a general tendency for attention to the more mild cues to be actively avoided, although the more severe pictures typically held attention. This provides support for the view that non-anxious individuals can adaptively prevent their attention being captured by mildly emotional cues but this control is overridden in most people as threat severity increases.

CE7.1.2 Evidence that biased processing has causal effects on mood

Although Mathews and colleagues have postulated that attentional and interpretative biases play a central role in the self-perpetuating patterns of information processing in anxiety disorders, until recently there has been no convincing evidence that this relationship was causal. Recently, however, techniques have been developed for inducing emotional processing biases in the laboratory, and have been used to reveal the conditions under which they can cause changes in vulnerability to anxiety.

In an initial series of experiments (Grey & Mathews, 2000) volunteers were presented with threat/neutral homographs as clues to solve word fragments (e.g. batter – in-ury or batter - pa-cake), or in the context of relationship judgements (e.g. Injury - batter. Related?). Participants were randomly allocated to decisions involving either threatening or neutral meanings of homographs, and then tested with new homographs not previously exposed. Both when tested with similar decisions as used in earlier, and with a completely new lexical decision task, these participants showed evidence that their prior experience continued to influence their interpretation of new homograph meanings. Most critically, in current experiments (in collaboration with Colin MacLeod), Mathews has shown that subsequent exposure to an ambiguously threatening event (videos of accidents) leads to different emotional consequences. Those exposed to negative homograph meanings reported increases in state anxiety, while those exposed to benign meanings did not. Post - experimental interviews indicated that participants were unaware of any connection between their prior exposure and later anxiety reactions.

In a parallel series of experiments, Mathews & Mackintosh (2000) have used more complex descriptions of real-life events, having threatening or benign outcomes determined by a final word. In some experiments, volunteers simply read these descriptions while imagining themselves in the situations, while in others they read the same passages up until the final word, which was presented in a to-be-completed fragment form. In all experiments, participants were randomly allocated to threatening or benign outcomes, and then read a new set of descriptions with ambiguous outcomes. Their interpretation of these ambiguous events was established indirectly using a recognition test involving negative and positive versions of the original items. This procedure has revealed a very robust interpretative bias that lasts at least into the following day. Another critical finding was that anxiety changed in a congruent direction when (and only when) training involved participants in the active generation of emotional meanings (e.g. by resolving the final word fragment).

In reviewing these (and other experiments on training attention), Mathews & MacLeod (2002) concluded that experimental induction of processing biases can readily be achieved in the laboratory, without the awareness of participants. The induction procedures themselves do not normally induce emotional changes directly (with some predictable exceptions), but do influence how later events are interpreted. When these interpretations have emotional implications for the individual concerned, they elicit congruent changes in mood. These findings thus provide the first evidence that processing biases can indeed be a cause of anxiety, albeit indirectly by influencing how new events are interpreted.

CE7.2 Modes of self-attention

Teasdale (1999c) drew attention to the apparently anomalous relationship of self-attention to the perpetuation and amelioration of emotional disorders. On the one hand, a tendency to focus attention on the self has been consistently associated with emotional disorders, particularly depression. On the other hand, interventions that involve individuals intentionally focusing attention on aspects of emotional experience lead to reductions in disordered emotion. Using the Interacting Cognitive Subsystems (ICS) theoretical framework, Teasdale suggested that this anomaly could be resolved by recognising the existence of different modes of self-focus. These modes are characterised by distinct configurations of processing resources (see project CE3), and, for that reason, are also characterised by distinct relationships to the perpetuation of emotion. The ICS analysis (Teasdale, 1999c) suggested that perpetuation of depression involves a ruminative mode of self-attention, focused on processing discrepancies between conceptual-level (propositional) representations of current and goal self-states. This analytical mode involves thinking about the self as a conceptual object. Conversely, therapeutic change involves a mode of self-focus controlled at a more schematic (implicational) level. This experiential mode involves less goal-related discrepancy processing. In this mode the subjective self is experienced directly as feelings, thoughts, and body sensations in the moment. Teasdale and colleagues have developed methods to induce experimentally these two modes of self-focus and have demonstrated differences in their effects on aspects of autobiographical memory.

CE7.2.1 Effects on overgeneral autobiographical memory in clinical depression

Measures of overgeneral autobiographical memory (OGM) (see CE5) predict the course of depressive disorders, and, for that reason, OGM has been assumed to reflect processes central to the maintenance of depression. Because OGM is shown by both acutely depressed and recovered patients, and is unrelated to the severity of depressed mood, it has been assumed to be a persistent, trait-like characteristic of depression-prone individuals. However, in collaborative experimental work Teasdale has shown, for the first time, that OGM in both depressed adults and children can be modified by manipulations of attentional focus as brief as 8 minutes (Park, Goodyer & Teasdale, submitted; Watkins, Teasdale & Williams, 2000; Watkins & Teasdale, 2001; Watkins & Teasdale, submitted). These findings suggest that the apparent stability of OGM in the depression-prone reflects its dynamic maintenance by processes that can be disrupted by competing tasks, rather than the trait-like characteristic, previously assumed. Further, these studies have identified the interruption of analytical, ruminative thinking as a feature of interventions that reduce OGM. From their findings, Watkins and Teasdale (2001) proposed that OGM reflects chronic ruminative attempts to analyse and understand current and past difficulties.

These studies of brief attentional manipulations in clinically depressed individuals have also provided an opportunity to examine the effects of analytical versus experiential self-focus on OGM, a variable known to be related to the maintenance of depression. Watkins and Teasdale (2001) induced analytical and experiential self - focus in clinically depressed individuals. The inductions had similar effects on depressed mood, but experiential self-focus significantly reduced the overgenerality of memories, compared to analytical self - focus. In a subsequent study (Watkins & Teasdale, submitted) in which the analytical and experiential inductions used identical items and differed only in the instructional set within which participants processed aspects of self-experience ("think about" versus "experience directly"), the same pattern of results was obtained. These results are consistent with Teasdale's (1999c) proposals that ruminative self-focus acts to perpetuate depression, whereas experiential self-focus can ameliorate it. The latter suggests that more extended training in experiential self-focus could be a valuable clinical intervention to modify depression. This suggestion is developed further in CE8.

CE7.2.2 Effects on the at-oneness of autobiographical memories

In parallel with the above studies of depressed patients, experiments in non-depressed individuals have examined the effects of ruminative analytical versus experiential self-focus on a novel measure of autobiographical memory. This measure is assumed to reflect affect-related discrepancy-based processing. Within Teasdale's (1999c) analysis, such processing is seen as a characteristic feature of ruminative analytical self-focus. It was assumed that the autobiographical memories most accessible at a given time provide a window into the processing configuration active at that time. Ratings of how "at one with things" individuals felt in their most accessible memories were used as a measure of goal-related discrepancy-based processing: low at-oneness was assumed to reflect high discrepancy processing, characteristic of a ruminative, analytic, form of self-focus. Consistent with this assumption, low ratings of at-oneness of autobiographical memories uniquely and substantially predicted high scores on dispositional ruminative self-focus and neuroticism in a sample of 130 normal volunteers (Teasdale & Green, submitted). Three experiments examined the effects of experimentally induced analytical self-focus versus experiential self-focus on the at-oneness of autobiographical memories. Compared with analytical self-focus, experiential self-focus consistently increased the at-oneness of autobiographical memories, while having no differential effect on the happiness or unhappiness of memories, or on mood. Putting the negative correlation of at-oneness with ruminative self-focus, observed by Teasdale and Green, together with the positive effects of experiential self-awareness on at-oneness observed experimentally, these findings support Teasdale's (1999c) suggestion that analytical self-focus and experiential self-focus are distinct forms of self-attention, with different functional properties. Further, the experimental findings in non-depressed individuals provide further evidence that, relative to analytical self-focus, experiential self-focus reduces a process (self-related discrepancy processing) assumed to maintain depression.

In summary, Project CE7.2 supports a distinction between analytical self-focus and experiential self-focus, and shows that experiential self-focus can reduce processes implicated in the perpetuation and escalation of depression. These studies provide an experimental foundation for the training in mindfulness (a form of experiential awareness) that is a central component of the innovative relapse prevention programme described in Project CE8.

Project CE8: Development and evaluation of clinical therapeutic procedures and processes

Scientific Direction: Teasdale (50%).

Research support: Green (10%).

Self-supported students: Ma (3 years, 100%).

Major depressive disorder is a lifelong, recurring condition. It follows that prevention of relapse and recurrence is a centrally important therapeutic challenge. Teasdale, in collaborative work, funded by external grants, has investigated the outcomes and therapeutic mechanisms of two psychological interventions for relapse prevention in recurrent depression. One, cognitive therapy (CT), is an established treatment. The other, mindfulness-based cognitive therapy, is a radically novel approach developed by Teasdale and colleagues on the foundation of prior experimental and theoretical work.

CE8.1 Cognitive therapy and the prevention of relapse and recurrence in residual depression

Depressed patients treated with antidepressant medication who still show residual symptoms of depression are at high risk of relapse. In a two-centre trial (Paykel, Scott, Teasdale, et al., 1999) 158 such patients were randomised either to continue with medication and clinical management, or, additionally, to receive CT. CT significantly reduced relapse by approximately 40%. This result is very important (and this trial was identified as one of MRC's highlighted achievements for the year 1999) as it is the first trial to show, unambiguously, that CT can reduce relapse, compared to continuing pharmacotherapy, in just those patients for whom it is most relevant. Effects of CT on relapse were not accompanied by reductions in background levels of depressive symptoms, suggesting that CT acted through reducing the escalation of symptoms at times of potential relapse, rather than through a generalised reduction in symptom levels (Scott, Teasdale, et al., 2000).

This trial also provided an opportunity to investigate the processes through which CT prevents relapse. CT explicitly aims to reduce belief in the content of negative thoughts and dysfunctional assumptions. It has been widely assumed that these changes in belief mediate the relapse prevention effects of CT. However, there has been a consistent failure to support this view empirically. By contrast, an ICS analysis (e.g.Teasdale, 1997a) suggests that CT works, not through changing belief in thought content, but through changing patients' way of processing, or relationship to, their negative thoughts and feelings. For example, the existence of two levels of meaning in ICS (CE3) suggests that representations at one level of meaning can concurrently be the topic of representations at the other level of meaning. This has particular advantages in analysing the role of metacognitive processing in the maintenance and modification of mood disorders (Teasdale, 1999b).

Teasdale's (1997a, 1997b) analysis suggested that increased metacognitive awareness (the ability to see negative thoughts and feelings as events in the mind, rather than identifying with them, or regarding them as necessarily true) is an important aspect of the shift in relationship to negative thinking effected by CT. To test this hypothesis, a memory-based measure of metacognitive awareness was developed and included in the above trial. Consistent with the hypothesis that CT prevented relapse through increasing metacognitive awareness, low metacognitive awareness predicted subsequent relapse, and CT significantly increased metacognitive awareness (Teasdale et al., 2002).

More detailed mediational analyses in this trial (Teasdale et al., 2001) provided further support for the view that CT prevents relapse by changing the way that depressive thinking is processed, rather than by changing belief in its content. First, CT significantly reduced measures of the form of thinking (the extent to which it was absolutistic or "black and white"); second, these measures predicted relapse; and third, the effects of CT on relapse could be accounted for by changes in these measures. By contrast, as in previous studies, measures of belief in the content of negative thinking failed to provide any evidence that changes in belief mediated therapeutic effects. This is the first time that effects of CT in preventing relapse in depression have been shown to be mediated by changes in any cognitive variable. It is particularly important, therefore, that mediation was demonstrated for a measure related to the way that thinking was processed, rather than its content.

This mediational analysis suggested that CT prevents relapse by teaching patients, in depressed mood, to switch out of an habitual ruminative mode of negative thinking into an intentional processing mode in which initial, dysfunctional, "automatic" cognitive products are reappraised using controlled processing resources. In quite separate work (conducted under CE5 but reported here), Sheppard and Teasdale (2000, submitted), using decision latency measures in novel experimental paradigms, independently identified a deficit in such metacognitive monitoring as a feature of acute major depression. Further, they showed that recovery normally involves a transition through a phase in which dysfunctional schematic products are effortfully re-appraised to produce more functional products, before more automatic access to functional schemas is established with full remission. These findings suggest that CT may be effective because it operates through reinforcing the use of a pre-existing meta-cognitive strategy.

In summary, this trial of CT for residual depression provided very important evidence for the clinical efficacy of CT in reducing relapse. It also provided the first peer-reviewed evidence demonstrating the mechanisms through which CT achieves these preventive effects. This evidence supported Teasdale and colleagues' proposals, derived from ICS, that CT works by changing the way in which negative thoughts are processed, rather than through changing belief in thought content. These proposals were the basis from which the novel preventive programme described in CE8 was derived.

CE8.2 Mindfulness-based cognitive therapy for prevention of relapse in recurrent depression

The differential activation analysis of vulnerability to relapse (CE5.1.3) suggests that prevention of relapse and recurrence in major depression requires that patients, particularly those who have experienced multiple episodes, learn how to prevent the escalation of negative, ruminative, thought patterns reactivated by dysphoria. In an analysis of the effectiveness of CT, Teasdale, Segal & Williams (1995) proposed that CT, although explicitly targeted on changing belief in depressive thoughts and assumptions, implicitly teaches patients to prevent escalation of rumination in dysphoria by switching to an intentional processing mode in which negative thoughts and feelings are treated as passing events in the mind, rather than as self or as accurate readouts on reality. The evidence in CE8.1 supports this analysis.

Mindfulness-based cognitive therapy (MBCT) (Segal, Williams, & Teasdale, 2002; Teasdale, 2000) is a radically novel, highly cost-efficient intervention, explicitly designed by Teasdale, Segal and Williams to teach recovered recurrently depressed patients the response prevention skills that the above analysis suggests are necessary, and that are taught, implicitly, by CT. Unlike CT, MBCT does not focus on changing belief in the content of negative thoughts. Instead, it teaches patients skills that allow them to intentionally disengage from negative, ruminative thought patterns reactivated by dysphoric mood at times of potential relapse. MBCT does this by training patients to bring experiential self-awareness (mindfulness) (CE7.2) to their thoughts, feelings and bodily sensations. In parallel, MBCT cultivates metacognitive awareness, the capacity to relate to thoughts and feelings as mental events.

In a three-centre clinical trial, 145 recovered recurrently depressed patients were randomised either to continue with treatment-as-usual or, additionally, to participate in the MBCT programme (Teasdale et al., 2000). For patients with 3 or more previous episodes of depression (77% of sample), MBCT significantly reduced relapse from 66% to 37%. For patients with only two episodes (23% of sample) MBCT was of no benefit. MBCT also increased metacognitive awareness (Teasdale et al., 2002), and reduced overgeneral autobiographical memory (Williams, Teasdale, Segal & Soulsby, 2000). This trial was the first demonstration that a group psychological intervention, administered in recovery, could significantly reduce relapse and recurrence in major depression. It was also the first multi-centre trial of a mindfulness-based clinical intervention.

A subsequent clinical trial (Ma & Teasdale, submitted) with the same design, replicated the finding that MBCT is a highly cost-efficient approach to preventing relapse in patients with 3 or more episodes: relapses were reduced from 78% to 36% for an average therapist contact of only 2 to 3 hours per patient. Again, patients with only two previous episodes failed to benefit from MBCT. This trial provided evidence to support the hypotheses (Teasdale et al., 2000) 1) that MBCT is specifically effective in reducing relapses triggered by dysphoria reactivating autonomous ruminative thought patterns, rather than those provoked by major life events, and 2) that this is the reason why MBCT is ineffective with patients with only 2 episodes; for these patients, relapse was primarily provoked by major life events. MBCT was also found to reduce measures of rumination, thought suppression, and salivary cortisol, compared to the control condition. A therapist manual describing the development, delivery, and evaluation of MBCT has been published (Segal, Williams, & Teasdale, 2002), and a scale to assess therapist adherence to MBCT has been developed and validated (Segal, Teasdale, Williams & Gemar, 2002).

MBCT has attracted wide attention internationally. For example, in 2001, Teasdale was invited by the US National Institute of Mental Health, as the only non-North American participant, to make a presentation on MBCT to an invited working group reviewing approaches to relapse prevention in major depression. In contrast to conventional CT, MBCT makes no attempt to teach patients to address belief in the content of negative thoughts. Instead, it trains patients to access a mode of intentional cognitive processing in which negative thoughts, feelings, and body sensations are regarded as passing objects of attention. The success of this programme in preventing relapse in recurrent depression supports this shift in therapeutic strategy, and opens up new directions for the development of therapeutic procedures that are complementary to existing cognitive therapy approaches across a wide range of disorders. This success also supports the general strategy, inherent in the Cognition and Emotion group, of basing therapeutic interventions on empirically grounded theoretical analyses of emotional disorders and their treatment.

AWARDS AND HONOURS

Dr P. Barnard was appointed to a Visiting Professorship in the Departments of Psychology and Computer Science, University College London, from 2002 to 2007. Dr T. Dalgleish received the May Davidson Award from the British Psychological Society in 1999/2000 for early career contribution to clinical psychology. He also became an Honorary Senior Lecturer in psychology at the Institute of Psychiatry in 1999, and holds a non-stipendiary research fellowship, at Clare Hall College, Cambridge from 1999 to 2002. Dr A. Mathews was appointed to a Visiting Professorship at the Institute of Psychiatry from 1997 onwards. Dr J. Teasdale was elected Fellow of both the British Academy and the Academy of Medical Sciences in 2000.

PUBLICATIONS

(Note: Some papers are included that were published prior to 1998. These represent relevant work that appeared during the interval between the last formal Unit Review and the current reporting period.)

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TRANSFER TO HEALTH SERVICE

The trials demonstrating the efficacy of mindfulness-based cognitive therapy (MBCT) carried out by Dr Teasdale and colleagues have led to the establishment of some MBCT programmes in the NHS.

EXTERNAL GRANTS

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3 COGNITION AND EMOTION GROUP PROGRESS REPORT

Overview

The aims of the Cognition and Emotion programme are 1) to increase basic understanding of the representation, elicitation, maintenance, and control of emotion, at neurobiological, cognitive, and computational levels of explanation, and 2) to apply that understanding to the analysis and treatment of disorders of emotion. Research spans a range from the detailed analysis of perceptual mechanisms of emotion recognition, using neuroimaging, neuropsychological, and cognitive methodologies, through to the development of novel therapeutic interventions and their evaluation in clinical trials. This breadth of inquiry is co-ordinated within multi-level theoretical frameworks developed by our group (e.g. Mathews & Mackintosh, 1998; Power & Dalgleish, 1997; Teasdale & Barnard, 1993). It is increasingly recognised that such frameworks are necessary for a comprehensive understanding of the multiple interacting processes that contribute to emotion production and control. Our research has generated a wealth of specific findings. Here, we preview some of the more important general conclusions that emerge from our studies. These conclusions offer guidance for deepening basic understanding, formulating further research, and improving patient care.

Neuroimaging and neuropsychological studies conducted in Projects CE1 and CE6 have produced critical new evidence converging on the conclusion that multiple brain systems interact in processing emotional information. In summary, some brain systems (e.g. amygdala, insula) have been shown to be involved in processing affective stimuli associated with specific basic emotions while others (e.g. medial frontal cortex) appear to be involved in a range of emotions, drawing on multiple sources to compute more complex emotional and social meanings. Yet others (e.g. anterior cingulate cortex and dorsolateral frontal cortex) are concerned with higher level control of both emotional and non-emotional processing. Differences in neurotransmitter receptor densities in some of these systems have been shown to correlate with trait differences in emotionality, providing a new means of testing theories of how emotions and personality traits are related. The propensity to experience emotions thus depends on the outcome of interactions among several different brain systems. The co-existence of specificity and generality of emotion-related brain functions is precisely what our multi-level analyses of emotion predict, and reinforces our strategy of combining detailed investigation of individual component systems, with the development of frameworks that specify how those components interact.

Work on recognition of emotional expression (Projects CE2 and CE6) illustrates how the detailed investigation of particular component systems can yield an elegantly simple model that captures key features of a range of functions. Building on earlier work on recognition of facial identity, research in the reporting period has shown that multidimensional principal component analysis provides compelling models. These can account not only for recognition of identity, but also of emotional expression, gender, the dissociation of identity and expression recognition, effects of emotional intensity, and the configural nature of expression processing. The success of this work indicates the potential fruitfulness of focusing analysis at the level of component systems.

At the same time, the strategy of focusing investigation on component systems and subsystems needs to be complemented by analyses that focus on the patterns of interaction between subsystems that support more complex functions. This is a formidable challenge. Project CE3 describes the early stages of development of a radically new approach to computational modelling which has explored the distributed control of exchanges between component subsystems within a wider, distributed system. This modelling work has been complemented by empirical work in both clinical and non-clinical populations. This has shown that important aspects of central executive function can be understood in terms of changes in the patterns of interaction between subsystems, rather than deficits or anomalies in the subsystems themselves. This work validates the potential usefulness of this unique approach to computational modelling. It indicates that we can now move forward to model further aspects of the exchanges between subsystems that our models suggest are of central importance in cognitive-affective function.

The interaction of automatic affective and controlled cognitive processing is particularly important in understanding the maintenance of affect. Project CE4 addressed instances of such processes associated with vulnerability to anxiety and depression, such as selective attention to threatening information, and perception of the more negative meanings of ambiguous events. These processes have the effect of making potential threats more intrusive, and in this way can maintain negative emotions. New evidence shows that opposing positive biases occur in healthy people, but are not present in anxious patients. A similar failure of positive bias can be induced experimentally, producing symptoms characteristic of anxiety disorders. In healthy individuals, task-irrelevant aversive stimuli are typically easily ignored, but work in this project has revealed that those vulnerable to negative affect are less able to disengage from such stimuli, and to inhibit or forget unwanted aversive meanings. These findings show that stable individuals are able to inhibit mildly aversive information, but that inhibition failure is associated with vulnerability to anxiety or depression, and that such processing causes congruent changes in affective symptoms. In demonstrating the importance of such failures of disengagement and inhibition, these studies point to a need to shift the emphasis in existing explanatory models. Rather than attempting to understand emotional disorders solely in terms of excessive activation of dysfunctional representations and processes, such accounts also need to recognise more clearly the importance of failures of appropriate inhibition.

Self-perpetuating emotion-related cognitive biases, such as those studied in Project CE4, have figured prominently in the multi-level analyses of emotional disorders developed by our group. Given the weight attached to these biases in the maintenance of emotional disorders, such as major depression and generalised anxiety, it is important also to understand their role in the initial onset of disorder, To this end, Project CE5 included extensive investigations of emotion-related cognitive biases in children with emotional disorders, many of whom were experiencing their first episodes, and in children who were at risk for disorder but who had not yet experienced an onset of the disorder. Findings demonstrated a pattern of disorder-specific cognitive biases that were very similar to those found in adult disorders, and that, in some cases could be shown to pre-date onset of disorder. These findings are important in suggesting that the identified self-perpetuating cognitive biases may be risk factors contributing to the initial onset of emotional disorders, rather than being primarily aftereffects of the experience of the initial episode.

Neurosurgical interventions on the intact human brain offer a rare opportunity to investigate the neural substrates of emotional disorder with the precision that is more usually associated with studies of experimentally induced lesions in animals. Project CE6 took advantage of such an opportunity in studying the effects of stereotactic subcaudate tractotomy for the relief of treatment resistant depression. The findings indicated a remarkable degree of specificity in the effects of this operation on neuropsychological measures. These effects were specific to reductions in patients' sensitivity to negative feedback information. This reduced sensitivity was shown only by patients who benefited clinically from the operation, and was not shown by either operated patients who failed to benefit from the operation, or by patients who did not receive the operation but whose depression improved as a result of pharmacotherapy. Such specificity is consistent with a causal role for reduced sensitivity to negative feedback in patients' clinical improvement, and for a role for heightened sensitivity in the maintenance of chronic depression. This study demonstrates the potential utility of this investigative strategy, as a way of elucidating simultaneously both the nature of depressive psychopathology, and the role of specific regions of the human brain.

Our multi-level analyses of emotional disorder implicate self-perpetuating cognitive-affective processing configurations in the moment-to-moment dynamic maintenance of states such as generalised anxiety and major depression. A crucial test of such models is the extent to which particular cognitive processing styles, that we believe play a causal role in perpetuating aversive emotional states, can be experimentally controlled. Project CE7 has shown that a threat-related attentional bias, of the kind assumed to maintain generalised anxiety, can be induced to previously neutral stimuli by associating them with threatening meanings, without participants' awareness. Further, practice in accessing negative meanings of ambiguous material was shown to lead to a related bias in processing new ambiguous information, together, most interestingly, with the development of a tendency to respond with anxiety to such information. These findings provide the first evidence that processing biases can indeed be a cause of anxiety. In major depression, brief attentional manipulations were found to reduce overgeneral memory, a characteristic feature of individuals prone to depression. These findings are consistent with the idea that overgeneral memory, like other features of depression, is dynamically maintained by self-perpetuating processes that can be interrupted, rather than an enduring trait-like feature, as was generally previously assumed. Further, this work has characterised two distinct modes of self-attention, one associated with perpetuation of depressive cognition, the other with its amelioration. Thus, laboratory-based manipulations can bring cognitive processes characteristic of emotional disorders, under experimental control. By manipulating the form of these processes, we have shown that they have causal effects on symptoms of emotional disorder. Further, this work has identified potential therapeutic processes for inclusion in clinical treatments.

An important motive for our more basic research on the interaction between cognition and affect in normal and disordered emotion has been to provide a firm basis for the development of new and more effective approaches to the treatment and prevention of emotional disorder. Project CE8 illustrates how our theoretical and experimental studies led to a radically different way to understand the effectiveness of an existing treatment for depression, cognitive therapy, which then provided the basis for the development of a new cost-efficient programme to prevent relapse in recurrent depression. Specifically, we gathered support for our hypothesis that cognitive therapy works through implicitly changing the mode of processing of negative thoughts and feelings, rather than through changing belief in the content of negative thoughts, as is generally assumed. This hypothesis guided the development of a programme explicitly designed to achieve the same ends as cognitive therapy, through systematic training in the control of modes of attention. In two clinical trials, we showed that this intervention, firmly rooted in theoretical and experimental work conducted within the Cognition and Emotion group, was highly effective in reducing relapse in recurrent depression, and did so in a way consistent with the processes that we had specified. This work validates our strategy of developing new approaches to patient care grounded in our basic research on cognitive-affective interaction.

Project CE1: Affect-related representations.

Scientific Direction: Calder (5%), Lawrence (70%), Mathews (20%), Teasdale (5%).

MRC-supported scientists: Murphy (100%)

Grant-supported scientists: Bishop (15 months, 100%), Potts (from January '02, 100%).

Research support: Green (5%), Keane (5%), Yiend, (20%).

The multi-level information processing analyses of emotion developed within the Cognition-Emotion group identify both sensory/perceptual and cognitive/interpretative levels of representation in the generation and regulation of affect, and in the interaction of cognition and emotion. The aim of project CE1 is to use functional neuroimaging and complementary techniques to identify the neural substrates of these interacting levels in cognitive-affective processing. Findings suggest that some brain systems are involved in processing specific types of sensory/perceptual emotional stimuli (e.g. amygdala, insula), while others (e.g. medial frontal cortex) probably draw on multiple sources of information to compute more complex emotional meanings. Yet other systems (e.g. dorsolateral frontal cortex) are concerned with higher level control of both emotional and non-emotional processing.

CE1.1 The cognitive generation of affect

The Interacting Cognitive Subsystems (ICS) framework (Teasdale & Barnard, 1993) suggests that the cognitive generation of affect depends on the integration of propositional meanings with perceptual input, to form schematic affective representations. Teasdale, in collaborative work at the Institute of Psychiatry, has conducted fMRI studies aimed at identifying brain networks mediating such cognitive generation of affect. These studies compared the activation elicited by presenting pictures and captions combined so as to represent a meaningful emotional event, or in a re-combined form so that they no longer meaningfully cohered. This methodology controls precisely for all aspects of stimulus materials other than the extent to which captions and pictures cohere. It follows that comparison of coherent and non-coherent caption-picture pairs identifies structures mediating the specifically meaning-related contribution to the generation of affect. Using this approach, Teasdale, Howard, Cox, Ha, Brammer, Williams & Checkley (1999) identified medial prefrontal networks related to the processing of schematic-level meanings and the cognitive generation of positive and negative affect. Networks activated were similar to those reported in other affect-elicitation imaging studies (see CE1.3); the importance of this study is the precision with which the contribution of complex emotional meanings to affect-elicitiation can be specified.

A subsequent study using the same methodology (Kumari et al., in press) replicated these findings for normal subjects, and compared them with treatment resistant depressed patients. Compared to the controls, patients showed significantly less activation in the identified medial prefrontal networks to positive caption-picture pairs, suggesting deficits in the processing of cognitively generated positive affect in treatment resistant depression.

CE1.2 Eye gaze processing

The direction signalled by another person's eye gaze not only carries information about where the other person is looking (i.e., attentional cues), but also that something, or someone, has captured the gazer's attention. Consistent with the latter, Baron-Cohen (1997) has proposed that the interpretation of gaze plays an important role in a normally functioning theory of mind (ToM) system. Calder validated this role by showing that a meta-analysis of functional imaging research demonstrated that both ToM and eye gaze tasks engaged a similar region of posterior superior temporal sulcus (STS) (Calder et al., 2002). In addition, he noted that a second, more prominent brain region associated with ToM, the medial prefrontal (MPF) cortex, had not been identified by eye gaze research. In collaboration with Lawrence, Calder identified methodological issues that might account for the absence of MPF activation in these experiments. He then conducted a PET study that controlled for these factors and addressed the neural correlates of processing direct and averted gaze (Calder et al., 2002). The results showed that the MPF regions associated with ToM were indeed involved in processing gaze, but particularly averted gaze. Moreover, because participants were not explicitly asked to attend to the faces' gaze, the study demonstrates that simply viewing a face with averted gaze is sufficient to engage the mechanisms involved in ToM. This provides the first demonstration that the mechanisms involved in processing another person's mind state are engaged automatically. The MPF regions involved were very similar to those implicated in the cognitive generation of affect in CE1.1, consistent with a role for these brain regions in the processing of affect-related implicit meanings, and contributions from such meanings to gaze-related affect generation.

CE1.3 A novel imaging meta-analytic approach to understanding the structure of neural emotion space

The conclusions that can be drawn from any single functional imaging experiment are, necessarily, limited. To overcome this difficulty, Murphy, Nimmo-Smith & Lawrence (Lawrence & Murphy, 2001; Murphy, Nimmo-Smith & Lawrence, submitted) have applied novel statistical techniques to the meta-analysis of very large numbers of functional imaging experiments. Using a variant of the Kolmogorov-Smirnoff statistic, they examined the distribution of patterns of activation foci in functional imaging experiments, and how these distributions relate to models of the neural representation of emotions. Using data pooled from over 100 experiments, they tested predictions made by categorical (e.g. basic emotions) versus dimensional (e.g. approach/avoidance; valence/arousal) frameworks. In support of basic emotions accounts, the distribution of activation foci associated with discrete affects (fear, anger, disgust) were significantly different from each other, and from happiness and sadness. In contrast, the activation peaks for happiness and sadness were not different from each other. In addition, fear, disgust and anger activations were maximal bilaterally in regions which, when damaged, are associated with selective deficits in processing these emotions (fear - amygdala, disgust - insula, anger - ventral frontal cortex - see CE6); whereas happiness and sadness activations tended to cluster in the anterior cingulate. Activation of anterior cingulate cortex was associated with the majority of emotions, with the exception of disgust, suggesting that this region plays a generic role in the processing of a range of affects - consistent with multi-level representation of emotion. There was also some support for a differentiation of emotions in terms of associated action tendency (approach / avoidance), but no evidence for coding based on valence or arousal dimensions.

CE1.4 Emotional associative learning

The study of reward learning in animals has revealed an interrelated set of limbic and cortical structures involved in reinforcement and motivation. Emotional associative learning in humans has not yet been much investigated from a similar neuroscientific perspective. Conditioned place preference is one of the most common procedures for assessing stimulus-reward associative learning in animals, and Johnsrude, Owen, Zhao, & Whitney (1999) have developed an analogous procedure for use with people. Using this procedure, Johnsrude, Owen, White, Zhao & Bobhot (2000) have shown that unilateral removal of the temporal lobe, including the amygdaloid region, in humans (for the treatment of epilepsy), abolishes either the formation or expression of such conditioned preferences. In contrast, patients with unilateral frontal-lobe removals were unimpaired. This result provides clear evidence that, in humans as in other animals, reward-related learning critically depends on a circuit involving inferotemporal cortex and the amygdaloid region.

CE1.5 Interactions of emotional and cognitive control systems in the brain

Interactions between emotional processing and cognitive control systems are assumed to play a central role in the maintenance and regulation of affect. Mathews & Mackintosh (1998) proposed that threatening representations (of stimuli such as fear-related pictures) receive additional activation from a threat evaluation system (involving the amygdala complex), so that they are more likely to capture attention. Such activation may be inhibited, if it would conflict with other current goals, by competing activation of task-related representations from a control system, involving medial and dorsolateral areas of the frontal cortex. Mild emotional distracters may thus be ignored, and only more severe threats will disrupt attention to ongoing tasks (Mackintosh & Mathews, in press). Unintended attention to threatening distracters, which characterizes individuals vulnerable to anxiety states, can thus arise due to a lower response threshold in the threat evaluation system, and/or relatively weak inhibition by the control system.

Using fMRI, Mathews and Lawrence investigated the neural correlates of encoding manipulations on threat related material, in high and low anxious subjects, to test predictions made by the above model. Subjects viewed sets of pictures without specific instructions, and other sets while performing tasks: either judging if the current picture is more fear-inducing than the previous one (emotional task); or if it required more preparation by the photographer (non-emotional task). Findings so far are that threatening pictures provoke more activation in the primary visual cortex, parietal regions, and amygdala than neutral pictures. A parallel psycho-physiological study employed a noise-induced startle response to index amygdala activation. Startle magnitude was augmented when viewing threatening versus neutral pictures, and this difference was enhanced by judgements of fear, but was abolished by the non-emotional judgement task. These findings suggest that affect-related amygdala activation can be modulated by conscious cognitive control.

In collaboration with Bishop, Brett and Duncan (attention group), Lawrence conducted an event-related fMRI study to investigate the role of different prefrontal cortical structures in the processing of emotional material. Using a task which requires matching pairs of houses in the presence of emotional distractors (fearful faces), combined with a trial structure manipulation (frequent versus infrequent distractors) known from previous work to manipulate levels of cognitive control, this study demonstrated a role for the anterior cingulate (affective division) in detecting the presence of response conflict engendered by the presence of emotional distractors. In contrast, the dorsolateral prefrontal cortices were involved in implementing attentional control. Differences in dorsolateral prefrontal cortex were also seen as a function of anxiety levels. This work showed, for the first time, that different structures (anterior cingulate and lateral prefrontal cortex) play dissociable roles in control of emotional material (Bishop, Duncan, Brett & Lawrence, in submission). Further, it showed that areas already known to be involved in controlling attention in non-emotional tasks (the anterior cingulate and dorsolateral frontal cortex) are also employed when controlling response to emotional information.

CE1.6 Individual differences in affective style and temperament and their neurobiological correlates

Better understanding of the neurobiological substrates of stable individual differences in temperament and affectivity is centrally relevant to improved models of psychopathology. One of the most powerful theoretical frameworks for explaining such individual differences and their relation to emotion systems is the reward sensitivity theory of Gray (Gray, 1982). Gray's model postulates two major dimensions of temperament, anxiety and impulsivity, that represent individual differences in the sensitivity of two neural systems involving processing of aversive (Behavioural Inhibition System, BIS) and appetitive (Behavioural Activation System, BAS) cues, respectively. Certain forms of psychopathology can be characterized in relation to these major axes of personality variation (Pickering & Gray, 1999). For example, a link between the positive symptoms of schizophrenia and BAS function has been proposed (Pickering and Gray, 1999) and clinical anxiety is thought to be related to high levels of BIS activity.

Lawrence, in collaboration with Goerendt, Rabiner, McGowan, Brooks and Grasby at MRC Clinical Sciences Centre, London, have shown that individual differences in serotonin 5HT1a receptor densities in the hippocampus and amygdala are associated with individual differences in BIS function (as measured by the difference between scores on extraversion and neuroticism), but not with neuroticism or extraversion per se (Rabiner et al., 2002a and unpublished data). These data are consistent with Gray's model.

An intriguing finding from these initial studies was that 5HT1a receptor levels were associated also with scores on the lie scale from the Eysenck Personality Inventory (Rabiner et al., 2002a). Although initially thought to be a measure of false but socially desirable responses, it has been known for some time that this factor is in itself a substantive aspect of personality, and individual differences in this trait (sometimes called defensiveness) have been related to lifetime risk of psychopathology. Rabiner et al., (2002b) have replicated this finding in a new group of individuals. The finding of a relationship between scores on the lie factor and 5HT1a receptor levels has implications for conceptualisations of a serotonin-linked trait as well as factors predisposing to risk of affective disorder, and suggest revisions to reward sensitivity theory will be required.

Gray's model also predicts that individual differences in BAS system function will relate to indices of dopaminergic activity. Lawrence, together with Goerendt and Brooks, MRC CSC, have used [18F]Fdopa and [11C]Raclopride PET to measure individual differences in dopamine uptake and D2 receptor status, and have found that measures of impulsiveness are correlated with ventral striatal activity, but only in male participants. In addition, they have used H2[15]O PET to map the structures involved in processing cues thought to activate the BAS (financial rewards), and the modulation of these structures by dopamine neurotransmission (studies in Parkinson's disease). This work has shown that ventral fronto-striatal circuits mediate BAS function, and these structures are less activated in unmedicated PD patients, especially those showing symptoms of apathy, but can be restored by treatments that increase dopamine levels. In addition, behavioural work has shown that these circuits mediate the incentive motivational (speed enhancing) effects of monetary rewards.

A neuropsychological study found that individuals with anorexia nervosa, a profound disorder of appetitive function, show highly selective deficits in reward-based learning, consistent with a rather specific deficit in a

BAS system. In contrast, they show no impairment on difficult pattern recognition memory tasks associated with medial temporal lobe function (Lawrence, Dowson, Foxall, Summerfield, Robbins & Sahakian, in press). Gray's model predicts an association between the neural systems implicated in BAS system function and the neurobiology of positive schizophrenic symptoms (Pickering & Gray, 1999). In collaboration with McGowan and Grasby (MRC CSC, London), Lawrence has used PET imaging (blood flow and [18F]Fdopa to image dopamine function) to test this hypothesis. In line with Gray's theory, schizophrenic patients showed increased [18F]Fdopa values in the ventral striatum, related to their degree of positive symptomatology. In addition, [18F]Fdopa values were correlated with performance on tasks requiring the use of stored regularities to guide behaviour (such as verbal fluency) (McGowan, Lawrence & Grasby, 2001b, submitted).

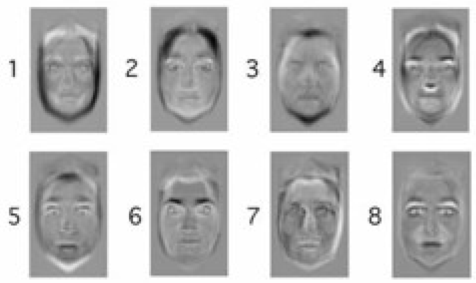
Project CE2: Recognition of emotion

Scientific Direction: Calder (55%).

Research support: Keane (55%).

The majority of research in facial expression processing has focused on the communicative value of facial expressions, and few studies have investigated the perceptual processes preceding this stage. As a result, there is no detailed model of facial expression recognition. Project CE2 addressed the perceptual mechanisms underlying the recognition of facial affect, with a view to developing a model of facial expression processing. The resultant multidimensional framework, based on principal component analysis (PCA), can account for all of the phenomena discussed below.

Figure 1: The first eight eigenvectors (eigenfaces) extracted from a PCA of the Ekman and Friesen (1976) pictures of facial affect. The eigenvectors have the same dimensionality as the original starting images so they can be displayed as visual images that have a ghost-like facial appearance. Note that the eigenvectors clearly capture aspects of the different expressions.



CE2.1 Front-end coding of facial expressions

It is generally agreed that facial identity recognition (who the person is) and facial expression recognition (what they are feeling) share the same front-end (perceptual) system. Previous research has shown that a principal component analysis (PCA) of the visual information in faces provides an effective front-end account of facial identity processing (Burton, Bruce, & Hancock, 1999). Hence, two critical questions are whether PCA can also support the recognition of facial expressions, and whether it provides a suitable means of coding a face's identity, expression, and sex within a single dimensional framework. Calder has addressed these issues by submitting the pixel intensities of pictures of facial expressions from the Ekman and Friesen (1976) series to a PCA (Calder, Burton, Miller, Young, & Akamatsu, 2001a) (Figure 1). The results showed that PCA provides a highly effective means of coding all three facial attributes. For facial expressions, the correct recognition rates and false positives derived from the principal components were well matched to human performance. In addition, the model exhibited properties of two competing accounts of facial expression processing (dimensional and category-based models), providing a means of reconciling what were generally perceived to be distinct theoretical accounts. Consistent with research showing that facial identity and facial expression recognition can be selectively disrupted, Calder found that cues to identity and expression were coded by largely separate sets of principal components. A similar dissociation was found for expression and sex, while, consistent with recent cognitive research, identity and sex were coded by largely overlapping sets of PCs (Ganel & Goshen-Gottstein, 2002). This research shows that linearised compact coding of human faces provides a highly plausible account of the psychological data.

CE2.2 Configural coding

It is well established that configural information (the relationships between facial features) plays an important role in coding a face's identity. However, its contribution to facial expression recognition is less well understood. In fact, some researchers have suggested that facial expressions are processed in a part-based (non-configural) manner (Ellison & Massaro, 1997). Calder addressed this issue using a composite paradigm (Calder, Young, Keane, & Dean, 2000d). Participants were slower to identify the expression in either half of composite facial expressions: that is, faces in which the top half of one expression (e.g., anger) was aligned with the bottom half of another (e.g., happiness) to create a novel expression configuration relative to a noncomposite control condition in which the two face halves were misaligned. These findings support the role of configural coding in facial expression recognition, and parallel the composite effect for facial identity (Young, Hellawell, & Hay, 1987). However, Calder also showed that the identity and expression effects operate independently of one another (i.e., the configural cues to these two facial attributes are qualitatively different). This research complements the findings of the PCA (see above) which showed that identity and expression are represented by separate principal components. In line with this observation Cottrell (California, San Diego) and Calder have shown that PCA provides an effective model of Calder's composite data (Cottrell, Branson, & Calder, 2002).

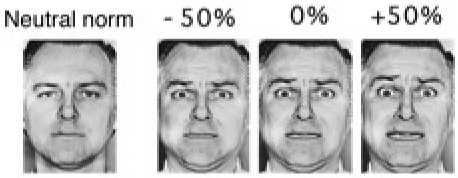
CE2.3 The representation of facial expressions

Facial expression recognition has been discussed in terms of two types of models. In category based systems, each expression is identified by activating a discrete representation. By contrast, in low dimensional accounts, facial expressions are identified by judging their values on two, or three continuous dimensions. These models have been applied to the recognition of emotion in general. However, as illustrated by the principal component analysis of facial expressions discussed above, they are also competing candidates for the perceptual representation of facial affect. To address this debate, Calder conducted a number of experiments using photographic-quality morphs (blends) and caricatures of facial expressions prepared using a computer-based procedure.

CE2.3.1 Categorical perception

Two studies used a categorical perception paradigm (Harnad, 1987) to address participants' perception of morphed facial expression continua ranging between pairs of facial expressions (e.g. anger and disgust; Calder, Young, Perrett, Etcoff, & Rowland, 1996a; Young et al., 1997). Results showed that all morphed images were consistently identified as the expressions at either end of the relevant continuum, with a sharp category boundary at the middle. In addition, pairs of morphs that straddled the category boundary were better discriminated than pairs of equal physical magnitude from either side of the boundary. Calder and Young have argued that these findings are consistent with the view that facial expressions are coded as discrete categories. In his work on PCA, Calder has proposed that facial expression categories can be viewed as clusters of vectors in a multidimensional space, with each cluster representing an attractor state for one facial expression (Calder et al., 2001a). Hence, categorical perception is consistent with a multidimensional account of facial expression coding. This research has also led to the production of a neuropsychological test of facial expression recognition (The Emotion Hexagon) that uses morphed facial expressions. To date, the test has been used in a number of studies, including those in CE6.

Figure 2: An example of a caricature (+50%) and anticaricature (-50%) image of an afraid facial expression. The images were produced by exaggerating (caricature), and reducing (anticaricature), the differences between the original afraid expression (0%) and a picture of the same model posing a neutral expression (left).



CE2.3.2 Emotional intensity

An important factor that distinguishes facial identity and facial expression is that the latter vary in intensity. Calder investigated the intensity issue using photographic-quality caricatures of facial expressions. Caricatures were produced using a computer graphics technique that exaggerated the physical differences between a particular facial expression (e.g., fear) and a picture of the same model posing a neutral expression. Similarly, anticaricature expressions were produced by reducing these differences (Figure 2). Subjects were significantly faster to recognise caricatured expressions relative to the original undistorted images, whereas anticaricatures produced slower recognition rates (Calder, Young, Rowland, & Perrett, 1997). An additional study showed a positive linear relationship between level of caricature and rated emotional intensity – but only for the emotional scale corresponding to the emotion displayed (i.e., fear caricatures were rated as expressing more fear, but not as more disgust, anger, etc.; Calder et al., 2000c). Caricatured expressions have provided a valuable stimulus material for Calder's collaborative functional imaging projects (see CE6). These studies mirror the findings discussed above by showing that caricatures of fear and disgust engage different brain regions, with changes in neural activity being positively related to level of caricature (Morris et al., 1998; Morris et al., 1996; Phillips et al., 1997; 1998). Calder has shown that caricature effects for facial expressions are best accounted for by an exemplar-based model of facial expression coding, analogous to the PCA architecture discussed above (Calder et al., 2001a; Calder et al., 2000c). In such a system, each expression category is coded as clusters of exemplars (vectors) in multidimensional space, and caricaturing operates by shifting the expression along the vector.

Summary: This research programme has addressed the perceptual processing of facial expressions from front-end analysis through to the point of representation. The results demonstrate that a multidimensional system based on a form of linear encoding analogous to PCA, provides a suitable metaphor for processing facial affect. Moreover, this single PCA-based system provides a model of coding a number of facial attributes (i.e., facial identity, expression, and sex). In addition, it can account for the dissociable effects observed for facial expression and facial identity processing (e.g., different configural cues for expression and identity), and single route coding of identity and sex (Ganel & Goshen-Gottstein, 2002). The same multidimensional metaphor also provides a suitable account of the effects of categorical perception, caricature, and configural processing described.

Project CE3: Multi-level representation and processing dynamics

Scientific Direction: Barnard (90%).

Research support: Ramponi (90%).

MRC-supported students: Battye (3 years, 100%).

Grant-supported students: Tavares (1 year, 100%).

Multi-level theories focus on different types of representation and the parts they play in the generation and maintenance of affective states. The need for theories of this class, their properties, and their potential for linking information processing to neural level analyses have been reviewed (Teasdale, 1999a). Such theories provide an explicit basis for the distinction between a traditionally cognitive, or propositional, level of representation, within which emotion-related material may be discussed rationally, and non-conceptual levels of representation and meaning that are directly linked to affect.

The Interacting Cognitive Subsystems architecture (ICS) is an example of a multi-level theory that is formulated with sufficient precision to support both empirical studies and computational research. It views central executive functions as an emergent property of reciprocal exchanges between one subsystem that represents specific meanings as propositions and another subsystem that represents implicational meaning. Implicational meaning is cognitive-affective and takes the form of abstractly encoded schematic models of self, others and the world. These bring together the products of propositional cognition and the products of sensory processing, including body states. Exchanges between two levels of representation act as a real-time control loop for ideation and memory access, without theoretical reference to general-purpose resources such as a unitary central executive or a limited capacity working memory system (Barnard, 1999).

As a system-level approach, exchanges among levels of representation within ICS can operate in a number of alternative configurations. The configurations differ in the parts played by processes in the propositional and implicational subsystems (Barnard, 1985). A process can operate in automatic mode, relying solely on its immediate input to generate an output. Alternatively, a process can be re-configured to use an extended representation of recent input (buffered mode), or it can access longer-term regularities stored in memory (record access). Propositional-implicational exchanges can be co-ordinated by buffering propositional meanings, and their specific content, or by buffering schematic meanings with their more generic properties. In the propositional mode, internal attention and experience is focussed on specific meanings, while in the implicational mode, it is focussed on more generic, and potentially affectively charged meanings. As with many other theories, dysfunctional ideation is assumed to call upon abnormal schematic models of self, others and the world. What ICS adds is the hypothesis that key properties of normal and dysfunctional processing arise from an interaction between schematic models and the alternative modes in which they are processed while attending to meaning or retrieving it. This dynamic approach led to what has now become an influential account of depression (Teasdale & Barnard, 1993). It links depression to a state of interlocked processing between two levels of meaning in which attention is predominantly focussed on the propositional meanings that are generated by depressogenic schematic models. The general hypothesis is that executive control of normal and dysfunctional ideation depends upon models and modes. Specific control parameters, such as the salience and extent of discrepancies, or rates of change in information content, are hypothesised to determine how use of modes is dynamically co-ordinated over time.

In the current reporting period specific empirical projects have investigated how schematic models and modes influence the executive control of ideation in healthy volunteers and in patient groups. Theoretical work has tackled the difficult problem of how to resolve the computational issues that must be addressed when modelling complex systems with distributed rather than centralised control, and several forms of novel computational approaches have been developed. Additional theoretical work extending the ICS account from depression to other psychopathologies is described in CE5.

CE3.1 Attention to meaning in healthy volunteers

In everyday life there is natural variation in the extent to which we attend to detailed aspects of meaning. When asked a question like "How many animals of each kind did Moses take into the Ark?" many people will answer "Two" - not noticing that the relevant Biblical figure was actually Noah (Erickson & Mattson, 1981). Both Moses and Noah fit the same schema and this kind of phenomenon can be taken to index the extent to which respondents adopt an executive mode in which they analyse propositional meaning, or rely on more generically encoded schemata or models. The Moses illusion reflects the fact that much useful ideation can occur simply by glancing at schematic models in implicational mode. If no global discrepancy in meaning is detected from the glance, then a response can be generated without switching to the more time-consuming propositional mode required to take a detailed look at specific meanings. As a background for studies of patient populations, we investigated this type of phenomenon in normal healthy volunteers using two paradigms, one involving question-answering and the other involving watching rapidly presented lists of words belonging to a generic category and detecting targets that belonged to a semantically specific category.

CE3.1.1 Modes, schematic models and question-answering

Laboratory studies of executive function in healthy volunteers are likely to have over-estimated the extent to which ideation works in the analytic propositional mode, and underestimated how use of schematic models constrains understanding. Most tests take repeated measurements on similar problems and thus encourage participants to develop special-purpose executive strategies to minimise error. We asked single unexpected questions requesting a single large number in between two bounds (e.g. Can you please give me a random number between one million and ten million?). Small differences in question phrasing invoked very different distributions of responses. These allowed us to determine the generic features of numbers, such as their magnitude, parity, and complexity, that had been attended to, and hence we could infer what schematic models had been activated by the different questions (Scott, Barnard & May, 2001). As with the Moses illusion, we found that volunteers often failed to focus their attention on the relevant bounds, and did not check their responses prior to generating them. They frequently erred by reporting numbers outside the requested range. A follow up study also varied question phrasing but this time varied processing load by increasing the length of the number sequence to be generated. Here, we found that executive error rates in healthy populations occurred with 50% of the volunteers under conditions of high load (Barnard, Scott, & May, 2001). In both studies we demonstrated that the kind of executive errors often committed by frontal or manic patients can be understood as phenomena that also occur within the range of normal processing, albeit perhaps at the extreme of that range (see also CE5.2.2). Both the occurrence and nature of, these errors can be understood as resulting from attention primarily being paid to generically encoded schematic models rather than propositional details.

CE3.1.2 Modes of processing meaning and the Attentional Blink.

In another series of studies, we developed a novel variant of the attentional blink (AB) paradigm (Raymond, Shapiro & Arnell, 1992). We asked volunteers to detect an instance of a semantic category (jobs/occupations) in rapid serial visual presentation where most of the words belonged to a category (nature words) unrelated to the target. Our procedure ensured that volunteers could only determine what was and was not a target by processing meaning. If the sequence included non-target distractors, (e.g. miser) that were related in meaning to a subsequent target, then report of that target was substantially impaired. While evaluating the precise meaning of the distractor, they missed the target much more frequently than in a control condition with no distractor. Only minor impairment occurred in response to a category change unrelated in meaning to the target category. To have an effect the distractor had to be semantically salient. We used a sophisticated form of statistical semantics called Latent Semantic Analysis (Landauer & Dumais, 1997) to index semantic relatedness and to eliminate a simple priming explanation. The results supported an explanation in which an initial glance at implicational meaning marks an item as salient and triggers an extended look at its propositional meaning (Barnard, Scott, Taylor, May & Knightley, submitted). This demonstrated that AB onset and duration could be taken to index the time course of processing generic and specific meanings. It also led to a more controversial conclusion. Results obtained in the standard AB paradigm with coloured letters are now potentially open to explanation based on purely semantic mechanisms.

CE3.2 Attention to meaning in depressed, manic and anxious states

Taken together, the question-answering and AB paradigms provided evidence that modes adopted when paying attention to two levels of meaning are open to measurement and varied systematically in healthy volunteers. Since implicational meaning encompasses affect, the same tasks can be used to investigate the effects of different emotional states on the executive control of attention to meaning as a function of hypothetical parameters such as rates of information change or personal salience.

CE3.2.1 Executive modes in manic and depressed states.

In depressed states, Teasdale & Barnard (1993) argued that an analytic, propositional mode is preferentially adopted when processing negative self-models. Repeated generation of the same thought also implies a low rate of change in generic self-models or representations, with rather more moment to moment change in specific propositions. We have also argued that a more experiential, schematic mode is adopted in mania where high rates of change in generic representation occur in the form of flights of ideas (Barnard, in press). Our theoretical analysis argued that attention moves to the level of meaning with higher rates of change. This predicts that the Moses illusion should be less likely to occur in depressed mood states than in elevated mood states. It follows that bipolar patients, who display both extremes and can act as their own controls, should detect false presuppositions more readily when depressed than when manic. This prediction was confirmed in a longitudinal study using a task in which the pragmatic implications of a preceding statement were questioned. Patients in a depressed state were more likely to detect a false presupposition than when they were in a manic state. Patients' ability to attend to successive non-semantic targets (i.e. digits), as indexed by the SART (Robertso, Manly, Andrade, Baddeley, & Yiend, 1997), showed comparable decrements in both states (Barnard, Palmer & Scott, & Knightley, submitted). Hence, a simple explanation based on general attentional mechanisms being more widely disrupted in mania than in depression could be ruled out, and our effect linked to the preferential adoption of different modes of processing meaning.

CE3.2.2 Executive modes and schematic models in anxious states.

The ICS analysis of alternative modes applied in processing two levels of meaning offers a novel theoretical perspective on the processing of threat-related material by people in anxious states. Monitoring for threat related material could plausibly rely on the mechanism taking brief glances at implicational meaning, while the engagement of attention with threatening material could involve taking a more extended look at propositional meanings. Task-related and individual difference variables should both influence a generic salience parameter controlling mode shifts. We investigated this possibility in a series of three studies using the attentional blink paradigm in which we introduced threat-related distractors.

We first showed that physical threat words, unrelated in meaning to the target category, were capable of capturing attention in the AB paradigm, but only for trait anxious individuals who were state anxious at the time. Furthermore, the serial position curves indicated that the blink for threat material occurred later, and was briefer in duration, than that obtained previously for distractors more highly related in meaning to the targets. This suggested that attention under these circumstances was captured but not followed by a detailed look of the kind that occurred in our earlier experiment with healthy volunteers (CE3.1.2). A second experiment showed that social threat words had only minimal effects, like those of a simple category change in our earlier experiments. The respective contributions of semantic similarity and threat-relatedness were then examined in a more sophisticated design that used Latent Semantic Analysis to index both threat-relatedness and semantic similarity. In a context where jobs/occupations are the targets, distractors like villain and miser both have high levels of semantic association to the target category, but differ in their threat associations. Words like seducer and vegetarian show low levels of semantic associations to targets, but again differ in threat associations. The results replicated the basic effects of both semantic similarity (see 3.1.2) and of threat. All these words capture attention significantly to a greater or lesser extent, but the time to taken to engage a detailed propositional evaluation of a distractor's meaning, the depth and duration of that evaluation, vary with indices of state and trait anxiety. Anxious individuals do not just show a deeper blink to threat. Rather, the way they pay attention to meaning follows different patterns over time. These studies showed that an adequate theory of executive aspects of attention to affect-related meaning will require detailed modelling of task-induced salience, personal salience attributable to alternative self-models, and parameters determined by current affective state (see CE3.3.1 below).

CE3.3 Depression, self-models & memory

In the ICS architecture, representations are preserved in both the short and long term in memory records linked to specific subsystems. Recall and recollection are intimately bound up with attention to different levels of meaning or form (Barnard, 1999). Properties of encoding and retrieval in depressed states are theoretically related to both modes of executive control and schematic models (Teasdale & Barnard, 1993). In the current reporting period, we have investigated relationships between executive mode and schematic models in depression.

CE3.3.1 Autobiographical recall in depressed adolescents

Working in collaboration with Park (Dept. of Psychiatry Cambridge), we investigated autobiographical memory in adolescents with major depression. Independent groups in episode or in remission were given a series of autobiographical prompts. Case grammar analysis, based on linguistic distinctions concerning the generic semantic roles assigned to human agents, was used to analyse the verbal protocols. We found that self-reference in natural discourse differed between individuals currently depressed and those in remission. Currently depressed adolescents made proportionately fewer references to self-as-agent in an event, more state-based references to self and self-experience, and they also exhibited heightened used of negation, when compared to those with a diagnosis but not currently depressed. This supports the hypothesis (Teasdale & Barnard, 1993) that the model in place changes on generic features, such as agency, when depression remits. Reference to self-as-agent was negatively correlated not only with depressed state but also with an index of ruminative response style. Hence this result extends previous research by demonstrating an effect using an implicit measure of self-modelling expressed in natural discourse, as opposed to those based on questionnaires. When compared to a matched non-clinical sample, both the depressed and remitted groups gave reliably more propositions that referenced content beyond the context cued, an index of non-specific, or overgeneral recollection within this paradigm. This result effectively confirms previous findings obtained with the standard Galton cuing paradigm but using a new measure. The amount of overgeneral, or non-context specific material produced did not correlate with measures of current state or rumination (Barnard, Park & Ramponi, in preparation). Whereas the standard Galton procedure simply differentiates specific and overgeneral memories, our more refined methodology suggests that some attributes of the schematic models in place vary with current state. However, the attributes that change do not appear to be those that lead to overgeneral memories, which implies that other attributes do not vary with current state. Plausible determinants of this contrast were pursued in the next study which examined recollection in both autobiographical and recognition memory for word lists.

CE3.3.2 Recollection, self-models, modes and dysphoric mood

Using non-clinical samples of dysphoric and non-dysphoric participants, we investigated whether or not autobiographical recollection and non-autobiographical recollection for word lists were governed by the same determinants. Interest was focused on an assessment of the contributions of two factors. A predisposition to use a propositional mode of executive control was indexed by a ruminative response style. This was predicted to be associated with the production of fewer specific autobiographical memories and poorer recollection of list items. Self-complexity has been hypothesised as a vulnerability factor for depression (Linville, 1987). Those with more complex schematic models are argued to be less vulnerable. In a previous reporting period we had shown that those with more complex descriptions of daily routines showed greater recollection of specific autobiographical events (Eldridge, Barnard & Bekerian, 1994). We therefore hypothesised a general relationship between the complexity of self-models and recollection. Those with more complex models should be able to elaborate processing of both autobiographical and non-autobiographical material, and hence show enhanced recollection. The effects of this variable should be independent of the mode of executive processing. The complexity of self-and other-models was assessed using the Levels of Emotional Awareness Scale (Lane, Quinlan, Schwartz, Walker, & Zeitlin., 1990). Autobiographical recollection was assessed using the standard Galton cueing technique, while recollection of emotional neutral word lists was assessed in the remember-know paradigm (e.g. Gardiner & Richardson-Klavehn, 2000). The same samples of volunteers were assessed on both tasks. The dysphoric group showed a substantial deficit in recollection of list items and also recalled fewer specific autobiographical memories. The two measures were related: those recalling fewer specific autobiographical memories also recollected fewer list items. In both tasks multiple regression showed that unelaborated schematic models and a ruminative response style independently predicted a substantial proportion of the variance in recollection, with dysphoria contributing little. From this we conclude that the properties of schematic models and modes of executive control are the principal determinants of impaired recollection across tasks, rather than depressed mood per se (Ramponi,& Barnard, submitted). Such an analysis provides a more precise foundation for developing computationally explicit models than those theories that simply attribute memory impairments to a deficit in controlled rather than automatic processing.

CE3.4 Addressing the challenge of modelling highly concurrent architectures

The development of computationally explicit models is particularly challenging in the domain of cognition and affect. Multilevel theories emphasise highly concurrent processing both within local networks and on the wider scale of multiple interacting subsystems. In the current reporting period three avenues of modelling research have been pursued.

CE3.4.1 Analysis and simulation of multi-component, concurrent architectures

For modelling interactions among multiple subsystems our approach has been to explore and develop concepts for systems analysis (Barnard, May, Duke, & Duce, 2000, 2001). We proposed four particular concepts to organise more refined analyses of the behaviour of complex information processing systems: the configuration of information processing resources, their capabilities, the requirements that must be met for those capabilities to work, and the mechanisms that control and co-ordinate resource use. These concepts support the development of methods, and notations for analysing the resource requirements of particular mental tasks (Barnard & May, 2000; May & Barnard, in press). They also provide the foundation for developing computationally explicit models of highly concurrent architectures where resources can be rapidly re-configured in real time.

In one form of modelling, production system techniques were reported that automate ICS-based theoretical reasoning (Barnard & May, 1999). A second approach used an augmented form of modal action logic to demonstrate how mathematics can give rise to formal proofs of the application of ICS in behavioural tasks requiring complex actions and the integration of multi-modal sources of information (Duke, Barnard, Duce, & May, 1998). In a third approach, we have used process algebra to develop a running computational model of the attentional blink phenomena (Bowman & Barnard, 2001; Barnard & Bowman, submitted). This implemented attention switching between two levels of meaning. It relied on the idea of monitoring salience by glancing at incoming implicational representations and then switching to a more detailed look at propositional meaning only for those items found to be salient. Our use of process algebra simulates mental operations at a level of abstraction rather higher than that afforded either by traditional connectionist or symbolic methods. It operates at a level of process exchange and control directly analogous to the box models of cognitive psychology. We believe that this novel modelling technique, and our specific model of the attentional blink, have both broken substantial new ground. By actively researching alternative modelling methods our commitment is to find the best way of modelling the behaviour of interacting subsystems, rather than focussing all our efforts around one modelling technology, such as symbolic, connectionist, or hybrid methods.

CE3.4.2 Relating the modelling of cognitive systems to the modelling of neural systems.

In parallel with the other strands of modelling research one of our PhD students (Battye) has developed a connectionist model of the emotional Stroop effect (Battye, Barnard and Page, submitted). This work identified problems with a prior connectionist model of the emotional Stroop (Matthews and Harley, 1996) and rectified them. One key insight obtained from this new model was that apparently conflicting psychological theories of the emotional Stroop effect can all be traced back to the activation of common pathways in an underlying connectionist model. Battye has also developed a connectionist model of the attentional blink effect that offers the prospect of accounting for related cognitive phenomena on the basis of common underlying mechanisms, and relating those mechanisms to candidate brain systems such as the anterior cingulate cortex (Battye & Barnard, 2002). Another graduate student (Tavares) is currently using animated vignettes to determine how schematic models that differ on affect related dimensions, such as affiliation or antagonism, differentially activate frontal and posterior brain regions.

The Barnard and Bowman (submitted) process algebra-based model of the attentional blink implemented two modes of processing meaning with a delay line mechanism for holding active representations. Delay lines, which are essentially a linear arrangement of circuits which pass information states "down the line," have already been proposed as plausible functional correlates for the network structures observed in, for example, cerebellar cortex (Abeles, 1991) and could equally well exist in other cortical areas. In the current reporting period we have completed an initial phase of research (Barnard, report in private circulation) that has worked out how a subsystem of cognitive processes, like those proposed in ICS, could emerge from interactions among neural delay lines. Oscillations in the build up of delay line content offer one means for predicting when evoked electrical potentials should occur in response to changes in salience parameters in tasks such as the attentional blink. The qualitative nature and number of delay lines needed to represent a principal components analysis of the material being processed can also form a basis for predicting patterns of brain activation. This particular outcome of the theoretical work in the current programme forms a key component of our future proposals summarised later under Emotion programme E3.

Project CE4: Interactions of "automatic" affective and "controlled" cognitive processing in the maintenance of affect.

Scientific Direction: Dalgleish (15%), Mathews (35%).

Grant-supported scientists: Ridgeway (2 years, 100%).

Research support: Yiend, (35%).

MRC-supported students: Rafter, (3 years, 100%), Wood (3 years, 100%), Yiend (3 years, 100%).

CE4.1 Attentional bias and anxiety

Individuals vulnerable to anxiety are more attentive to threatening cues than are less anxious individuals (see Mathews & MacLeod, 1994). The methods used in previous studies have not enabled a distinction to be made between attentional engagement (a process in which attention is initially captured by stimuli) and attentional disengagement (in which attention is removed from one object or location and allocated elsewhere).

Engagement and disengagement may involve different brain systems, and establishing which is most involved in differential attention to threatening cues could have implications for modifying vulnerability to anxiety (see Project CE7).

Yiend & Mathews (2001a) investigated this issue using a method developed by Posner, in which a single emotionally neutral cue stimulus indicates the location of a target that follows. These so-called valid trials lead to faster detection of the target, while occasional invalid trials (in which the target appears in an alternative location) lead to slowing due to having to relocate attention. When the cues were pictures having threatening or neutral content, anxiety-prone individuals were particularly slow relative to controls in the invalid trials, but only when the pictures were threatening. The distinction between anxiety-prone groups was present when cues were displayed for 500ms but was reduced after 2 seconds. It was concluded that the attentional bias in anxiety involves a difficulty in disengaging attention from threatening cues at early stages of processing.

In a further series Mathews, Fox, Yiend & Calder (submitted) showed that this extends to locations having threat connotations. Faces with neutral or fearful expressions were displayed centrally, with eyes gazing to the right, left, or straight ahead. Target letters appearing randomly to the left or right, were detected more slowly when gaze had been directed to the other location than in the direction of gaze. In highly anxious individuals, target detection was particularly speeded in valid trials, when targets appeared in the direction indicated by a fearful (rather than neutral) gaze, and was particularly slowed in corresponding invalid trials. There was no such distinction due to fearful expression in low anxious individuals. It can be concluded that attending to the direction of another person's gaze is relatively automatic, and that the attention of anxiety-prone (but not low anxious) individuals is more strongly guided by eye gaze when a fearful expression implies the presence of danger. This evidence supports further the view that the attentional processing biases associated with vulnerability to anxiety will increase awareness of potential dangers, and thus may serve to maintain anxious mood (see also CE7).

CE4.2 Attention to threat in patients with life-threatening disease

Work on the prediction of anxiety in breast cancer patients (supported by a grant from the CRC to Mathews) has now been completed. A number of measures obtained immediately prior to diagnosis, including a measure of attention to emotional words, were predictive of distress four months later. These results show that patients who are prone to anxiety and health worry prior to diagnosis will continue to experience relatively greater emotional problems on follow up (Mathews, Ridgeway, Warren & Britton, 2002). These data have implications for predicting which patients may profit from anticipatory counselling following diagnosis of cancer.

CE4.3 Interpretation of emotional ambiguity

With Hirsch at the Institute of Psychiatry (London) Mathews has investigated the extent to which social phobia is associated with "on-line" interpretation of ambiguously threatening social events. Based on earlier work (Hirsch & Mathews, 1997), it was supposed that people without severe social anxiety typically attend to external cues (e.g. others' reactions), and tend to make positive inferences about their own social performance. In contrast, socially phobic individuals appear not to make such on-line inferences, either positive or negative, perhaps because their processing resources are depleted by anxiety and/or diverted to internal cues. Nonetheless, social phobics judge their own social performance harshly, presumably based on their prior expectations and internal feelings rather than external information.

To test this hypothesis, social phobic patients and non-anxious controls were asked to read descriptions of ambiguously threatening social events (interviews) while imagining themselves in those situations (as the interviewee). At unpredictable points in the text they made speeded lexical decisions for words that matched either a possible positive or a negative inference. Relative to an unambiguous control condition, at ambiguous points in the text non-anxious individuals were slower to endorse negative (but not positive) words matching possible inferences. Social phobics were always slower at ambiguous points than when the text was unambiguous. These data are consistent with the view that normal positive inferences are blocked in social phobia, and that this may contribute to the persistence of anxiety even in benign situations (Hirsch & Mathews, 2000).

One reason that social phobics fail to make positive inferences is that they report being distracted by negative images of themselves in social situations. When trained to replace these negative images with more benign versions, social phobics' anxiety decreased, and this improvement was apparent to blind observers of their social performance (Hirsch, Clark, Mathews & Williams, in press). Furthermore, when non-phobic volunteers were trained to hold negative self-images of themselves in mind, they came to resemble social phobics in failing to make normal positive inferences about social situations. It thus appears that an internal focus of attention on negative images both enhances anxiety and blocks protective positive inferences in social phobia.

CE4.4 Inhibitory processes and emotion

Mathews has explored negative priming of emotional and non-emotional words as a possible index of the ability to suppress responses to previously attended emotional words. Such failures of inhibition have previously found to be characteristic of Obsessional Disorders. Negative priming refers to the finding that when two items are presented with only one to be selected for report, it takes longer to name an item that was ignored in the preceding trial. Theoretical accounts of this phenomenon suggest that prior ignoring of the later to-be-selected item is crucial. In a novel procedure originally developed by MacDonald, Joordens, & Seergobin (1999), two words are presented together for a comparative judgement (e.g. which animal is larger?). In the critical trials, the non-selected item in a preceding trial becomes the to-be-selected item in the current trial. MacDonald et al. claimed that prior attention to the non-selected item did not prevent negative priming, but actually enhanced it. Mathews, Mackintosh & Holden (in press) found that, to the contrary, correct matching of ignored repetition and control item content revealed no negative priming at all if the to-be-selected items were previously attended and then rejected. Earlier conclusions from studies using this method, suggesting that Obsessive Compulsive patients show large negative priming effects (implying intact inhibitory processes) are thus invalid.

Mathews and Dalgleish (Wood, Mathews & Dalgleish, 2001) used a different technique to investigate the prediction that emotionally vulnerable individuals have particular difficulty in the inhibition of emotional processing. In a series of experiments, a reading task was performed that required the suppression of emotional or neutral meanings. Participants read sentences, some of which ended in threat/neutral homographs (e.g. Some puddings are made using batter) and were then required to decide if another word was related to the meaning of the sentence (e.g. injury). In these critical sentences, the threatening meaning was irrelevant and so must be rejected. Decisions involving homographs were significantly slowed relative to control sentences. When threatening (rather than neutral) meanings had to be suppressed, anxious participants made more errors and were also sometimes slower than control groups. It was concluded that inhibition of threat meanings may be more difficult in anxiety-prone individuals, consistent with the difficulty they experience in disengaging attention from threatening locations (see also Yiend & Mathews, 2000a).

This difficulty in inhibiting congruent emotional material in individuals prone to emotional problems was further investigated by Dalgleish and collaborators in patients with clinical depression using a directed forgetting (DF) methodology (Power, Dalgleish & Claudio, 2000). The DF paradigm requires individuals to try to forget information that they had previously been instructed to remember. The DF literature shows that successful forgetting in this context involves direct inhibition of the to-be-forgotten material. In this series of studies depressed and control participants were instructed to forget emotional and neutral material. DF was measured relative to a (remember) control condition in which no instruction to forget was given. The data showed that the depressed patients, but not the controls, showed no DF effect for emotional words. This provides further evidence of a difficulty in inhibiting emotional information in vulnerable and clinical groups.

Dalgleish and Mathews (Dalgleish, Mathews & Wood, 1999) outlined a theoretical framework for conceptualising inhibitory processes in cognition-emotion relations that rested on the distinction between automatic and controlled cognitive processing. A two-by-two taxonomy of inhibitory processes was outlined involving automatic and controlled processing of emotional cognitive content and automatic and controlled processing of emotional feelings and behaviours. Dalgleish (in collaboration with Andrews at the University of Essex) investigated this controlled/automatic distinction in a large sample of emergency service workers who were asked to respond to test items describing different putative ways in which they inhibited aspects of affect in relation to a specified traumatic event. Two clear factors emerged reflecting controlled (e.g. Do you make an effort to not talk about what happened?) and automatic (When you go over the event do your emotions feel numb?) inhibition processes. These factors significantly predicted levels of post-traumatic stress in a longitudinal study of a subset of the original sample. The factor structure was confirmed in an additional study of patients with eating disorders who had experienced traumatic life events (Andrews, Joseph, Troop Van Rooyen & Dalgleish, submitted).

Project CE5: Multi-level analyses of emotional disorders

Scientific Direction: Barnard (10%), Dalgleish (60%), Teasdale (20%).

Research support: Golden (80%), Green (10%), Ramponi (10%).

MRC-supported students: Dunn (3 years, 100%).

Grant-supported students: Sheppard (3 yrs,100%), Du Toit (2 yrs, 100%), Bishop (3 yrs, 20%).

Unique features of the work of the Cognition and Emotion group include: (1) integration of basic research on the interaction of cognition and emotion; (2) the development of comprehensive, multi-level, information processing theoretical frameworks on the basis of that research; (3) the development and investigation of analyses of specific emotional disorders within those frameworks; and (4) application of these analyses to understanding and developing psychological treatments for emotional disorders. Work in Project CE5 in the report period has taken forward step 3, multi-level analyses of emotional disorders, in two new directions: (a) inclusion of a developmental perspective; and (b) applications to new disorders.

CE5.1 Developmental aspects of emotional disorder

Multi-level analyses of emotional disorder in adults (e.g. Mathews & Mackintosh, 1998; Power & Dalgleish, 1997; Teasdale & Barnard, 1993) focus on the way that self-perpetuating patterns of information processing, frequently including mood-related cognitive biases, contribute to the onset and maintenance of disorder. For example, increased accessibility of self-devaluative material in depressed mood in individuals vulnerable to major depression is assumed to contribute to the maintenance and escalation of those moods; attentional biases to threat in anxious individuals are assumed to contribute to the development of generalised anxiety disorder. It is assumed that these self-perpetuating patterns are learned, but there has been very little research investigating the cognitive processing of emotional information in child and adolescent emotional disorders to determine when, developmentally, these patterns are established (Vasey, Dalgleish & Silverman, in press). Such research is important because in other areas of developmental psychology, there is evidence that cognitive processing follows a clear developmental course and is markedly different in younger groups relative to adults across a number of paradigms and cognitive domains.

CE5.1.1. Cognitive biases in childhood and adolescent emotional disorders

Dalgleish, with colleagues at the Institute of Psychiatry, carried out a large set of studies to address the following questions: 1) Do processing biases for emotional information exist in younger populations with emotional disorders? 2) If so, to what extent are they similar to such biases in adult samples? 3) What is the developmental course of such processing biases? The research involved 3 clinical samples of children and adolescents with diagnoses of Major Depressive Disorder (MDD), Generalized Anxiety Disorder (GAD), and Posttraumatic Stress Disorder (PTSD). The cognitive tasks were similar to those used with adult disorders and included measures of attention (the dot probe paradigm and the modified Stroop task), recognition and recall memory (for emotional words and trait adjectives), prospective cognition (probability estimates for future negative events), and the interpretation of ambiguity (homograph interpretation).

The most striking finding of these studies was that childhood and adolescent emotional disorders were each characterised by particular biases in processing emotional information that were very similar to the biases shown in corresponding adult disorders, and different from the pattern of biases shown in other disorders (Dalgleish et al., in press). The GAD and PTSD groups exhibited clear attentional and interpretative biases for threat-related material: (Dalgleish, Moradi, Taghavi, Neshat-Doost & Yule, 2001; Moradi, Taghavi, Neshat-Doost, Yule & Dalgleish, 1999a; Taghavi, Dalgleish, Moradi, Neshat-Doost & Yule, in press; Taghavi, Moradi, Neshat-Doost, Yule & Dalgleish, 2000; and Taghavi, Neshat-Doost, Moradi, Yule & Dalgleish, 1999). In contrast, attentional effects were absent in the MDD sample (Neshat-Doost, Moradi, Taghavi, Yule & Dalgleish, 2000; Neshat-Doost, Taghavi, Moradi, Yule & Dalgleish, 1997). Conversely, MDD children and adolescents, and a sub-clinically depressed sample, exhibited memory biases for negative self-encoded material (Neshat-Doost, Taghavi, Moradi, Yule & Dalgleish, 1998; Bishop, Dalgleish & Yule, submitted), but such biases were not shown by the GAD and PTSD children. The broad similarities between the cognitive biases shown by adult and childhood presentations of individual emotional disorders suggest that the disorder-related self-perpetuating processing patterns to which these biases contribute can become established relatively early in development. The main difference between the findings observed by Dalgleish and colleagues and previously reported findings in adults was that, on the prospective cognition measure, GAD, MDD and PTSD children, unlike their adult counterparts, showed no tendency to estimate negative events as more likely to happen to themselves than to others (Dalgleish, Moradi et al., 2000; Dalgleish, Taghavi et al., 1997). Follow-up studies suggested that the lack of a negative self-referent bias in clinically distressed children and adolescents reflected the operation of strategic inhibition mechanisms that served to protect the young patients from distressing material (Bishop, Dalgleish, Nimmo-Smith & Yule, submitted; Dalgleish et al., 1998; Dalgleish, Wood & Yule, submitted).

The developmental course of the different forms of processing bias in younger clinical groups was investigated using regression techniques. These showed that, within the age range studied (8 to 18), there was no evidence for a developmental progression in the measures of attentional bias, suggesting that these biases are established early and are relatively constant subsequently. In contrast, the strength of the relationship between depressed mood and memory bias in the MDD sample increased significantly with age. This finding is consistent with the hypothesis that such processing is underpinned by negative schematic self-representations. Other developmental evidence would lead us to expect that such representations would become more elaborate over development in ways that would increase self-referent memory biases.

CE5.1.2 Overgeneral autobiographical memory in major depression

In overgeneral autobiographical memory (OGM) individuals, asked to recall memories of specific events, produce, instead, categoric descriptions summarising repeated instances of such events. OGM occurs in major depression, predicts the course of this disorder, has been linked with cognitive avoidance and rumination (CE7), and is assumed to reflect core aspects of depressive psychopathology. All previous studies of OGM have been in adults. Teasdale, in collaboration with Park and Goodyer (Park, Goodyer & Teasdale, 2002) has demonstrated, for the first time, OGM in first episode major depression in adolescents. This finding is important in demonstrating that OGM is not an aftereffect of previous episodes of depression, and that it characterises developmentally early forms of major depressive disorder just as much as adult forms.

The tendency to generate overgeneral autobiographical memories has been associated with reports of childhood abuse in depressed patients (Kuyken & Brewin, 1995). In order to disentangle the relationships of depression and early trauma to OGM, Dalgleish, Tchanturia et al. (submitted) examined OGM in a group of patients with eating disorders for whom the primary diagnosis was not depression, but who, nonetheless, reported moderately high levels of both childhood abuse and depression. These patients generated more OGMs than controls, and the degree of OGM was positively associated with levels of self-reported abuse, even when levels of current depression were controlled for. These data, along with those of Kuyken and Brewin (1995) indicate that perceived early trauma, as well as significant levels of depression, are important contributors to OGM.

CE5.1.3 Cognitive vulnerability to first episode major depression in children and adolescents

Teasdale's (1988) differential activation hypothesis suggests that vulnerability to major depression is related to the kind of negative thinking patterns activated in states of mild depressed mood, rather than to the more trait-like aspects of thinking style emphasised by previous hypotheses. Activation of such patterns by current depressed mood is assumed to reflect a history of association between negative thinking and depressed mood in the past. This hypothesis can account for the observed progressive increase in risk for further episodes of depression with every consecutive episode experienced; each such episode provides further opportunities for associations to be formed between depressed mood and negative thinking. Studies in adults consistently support the differential activation hypothesis: recovered depressed patients (known to be at high risk for depression) show more negative depressogenic thinking than controls when assessed in induced or natural depressed mood, but not in non-depressed mood. It is not possible to tell from such studies whether the tendency for depressogenic thinking to be activated in dysphoria also preceded patients' first episode of major depression, constituting a prior vulnerability, or whether it was primarily a consequence or "scar" of earlier episodes. To address this issue, in work with Goodyer and colleagues (Kelvin, Goodyer, Teasdale & Brechin, 1999), Teasdale examined the thinking patterns of high emotionality children, known to be at risk for depression, who had not yet experienced an episode of major depression. As in adults, in induced depressed mood, high risk children showed more globally negative self-referent thinking than low risk children, but the groups did not differ in neutral mood. These findings demonstrate, for the first time, that the tendency to switch in depressogenic thinking in dysphoria constitutes a prior vulnerability for major depression.

CE5.1.4 Everyday memory in children and adolescents with PTSD

Research in adults with PTSD has shown that they present with impaired memory functioning (e.g. Yehuda et al., 1995) on a range of neuropsychological tasks. However, no such research has been carried out on younger populations. This is important because children and adolescents with PTSD are normatively pursuing their education and any impairments in memory, however short-lived, could have profound long-term consequences. Dalgleish and collaborators therefore examined memory functioning in children and adolescents with PTSD using the Rivermead Behavioural Memory Test, a set of tasks that taps everyday memory processes (Moradi, Neshat-Doost, Taghavi, Yule & Dalgleish, 1999b). Overall, the PTSD youth showed poorer memory performance than the controls. In particular, they were worse on tests of prospective memory where they had to remember an intention to carry out an act. These data suggest that attention needs to be paid to everyday cognitive functioning in young trauma survivors.

CE5.2 Applications to new disorders

CE5.2.1 Seasonal depression

In Major Depressive Disorder with Seasonal Pattern (MDD-SP), or seasonal depression, patients are in episode in the winter and in remission/recovery in the summer. Because variation in this disorder is so closely linked to biologically relevant seasonal rhythms, it is often assumed that these variations may be more directly biologically determined than in more common forms of unipolar depression. For this reason, Dalgleish used the study of seasonal depression as an opportunity to examine the generalisability of previous findings in unipolar depression to a condition that was clearly related, but that might have a different aetiology.

Dalgleish, Spinks, Kuyken and Yiend, (2001) found that, unlike patients with typical major depression, seasonally depressed patients did not differ overall from healthy controls on overgeneral autobiographical memory (OGM) when the 2 groups were compared in the winter, when the seasonally depressed patients were symptomatic. This lack of a significant cross-sectional OGM effect in seasonal depression was surprising given that the performance of seasonally depressed patients on other cognitive measures such as attributional style (Levitan et al., 1998) is similar to that in non-seasonal depression. Further, winter OGM scores, although not significantly elevated in the seasonally depressed, did predict the extent to which these patients recovered on observer-rated symptoms of depression the following summer. It was hypothesised that seasonal depression is not associated with fundamental shifts in elaborative cognitive processing, as indexed by explicit memory tasks, while nevertheless being associated with negative biases on tasks with a large self-report/response bias component, such as questionnaire measures. This idea was examined in a follow-up study (Dalgleish, Spinks, Golden & Du Toit, submitted) in which performance on a different memory measure - recall memory for trait adjectives - and on a self-report measure - the attributional style questionnaire (ASQ) - were assessed in healthy controls and a group of seasonally depressed patients in the winter when they were symptomatic. Again, patients were followed up in the summer and symptoms of depression were assessed by interview. The MDD-SP group differed from controls on the ASQ (in the predicted depressogenic way) but not on the recall measure. However, as with OGM, recall of self-referent negative adjectives predicted later symptom outcome. These studies suggest (a) that aspects of the mnemonic processing of emotional information in seasonal depression play an important role in the maintenance and recovery from the disorder but (b) that seasonal depression seems to differ from non-seasonal depression in that it is not associated with overall biases in memory for emotional information, as measured by both autobiographical recall and recall of trait adjectives. This may be because the aetiology of seasonal depression is more closely associated with biological factors than with cognitive ones (Dalgleish, Rosen & Marks, 1996).

CE5.2.2 Four sources of variation in dysfunctional ideation and affective states

ICS has previously been applied to the analysis of unipolar major depression (Teasdale & Barnard, 1993; and see CE7 and CE8). Barnard (in press) has extended the ICS analysis of symptom expression to a wider range of cognitive-affective psychopathology. He identified four theoretical sources of variation in the processing of propositional and implicational levels of meaning: Self-models, modes, how they are switched as a function of control parameters (e.g. salience, rate of change), and the consequences of asynchronous exchanges between subsystems. The schizophrenic spectrum of symptoms was related to the consequences of asynchronous exchanges between two levels of meaning. The symptoms of mania were related to high rates of change in implicational representations and to a predominance of experiential buffering at this level of representation, rather than the analytic buffering of propositional representations linked to depressive states. This illustrated how different, yet overlapping constellations of symptoms can arise when specific properties of executive processing move outside their normal range of operation. Some of the evidence leading to or predicted by this analysis was summarised in section CE3.

CE5.2.3 Theoretical modelling of PTSD

Dalgleish (submitted-a) has reviewed the major cognitive theories of PTSD and argued that they represent a paradigm case for the evolution of theorizing in psychopathology from single 'level' associative network or mental schema models of disorder to the types of multi-representational architectures that have been developed in the Cognition & Emotion group - SPAARS (Power & Dalgleish, 1997) and ICS (Teasdale & Barnard, 1993). This paper argues that three core representational systems (schemas, propositional representations, and associative representations) are necessary to provide comprehensive accounts of a range of psychopathology, using PTSD as the paradigm case. However, the cognitive theories of PTSD are called to account for their underspecification of the mechanics of theorising, for example how information is transferred from one type of representation to another, and this is targeted as a major item on the theoretical agenda.

CE5.2.4 Counterfactual reasoning in trauma survivors

A key feature of the clinical presentation of trauma survivors is the experience of intrusive and distressing thoughts about the original traumatic event. Often these thoughts are of a counterfactual (CF) nature whereby individuals try to imagine how the event might have turned out differently if a significant aspect had been different - mental undoing (Dunmore, Clark & Ehlers, 1999). Events can be mutated or undone in an upward direction to provide a better outcome (e.g. "if only I had not gone out that day then the accident would not have happened") or in a downward direction to provide a worse outcome. Mutations can be about self-related or other-related behaviours. Upwardly mutating the event has negative affective consequences as the individual is presented with an imagined way in which the trauma could have been avoided or ameliorated. Despite this emotional cost associated with upward mutations, clinical anecdotal evidence suggests that these are the most common form of CF intrusion in Posttraumatic Stress Disorder (PTSD).

Dalgleish (submitted-b) investigated this issue empirically in trauma survivors with and without PTSD to determine whether upward CFs were indeed normative in the disorder and, if this was the case, to examine what the function of such CFs might be. The first study revealed that trauma survivors did invariably make upward, self-referent CFs about their trauma, even though they had minimal control over the unfolding of the traumatic event at the time. However, the second study showed that this pattern was the same regardless of PTSD status. It was hypothesised that this pattern of CF reasoning might reflect attempts by all trauma survivors to integrate an element of self-control into their representation of the trauma by hypothetically mutating aspects of their behaviour such that the trauma could have been prevented. This cognitive gain might outweigh the negative affective cost of such CFs. A third study investigated whether this CF style transferred to events other than the original trauma and whether it varied with the objective controllability of the event. Trauma survivors and never-traumatised controls generated CFs to high- (car crash) and low-controllability (hurricane) accident scenarios. The results revealed that trauma survivors generated self-referent CFs to both high- and low-controllability scenarios. This was again independent of PTSD status. In contrast, controls showed this pattern for high controllability events, but not for low-controllability events, where the CFs were more likely to be other-referent.

It remained possible that this prevalent, self-referent CF style in trauma survivors was a function of priming of the original trauma memory by the research recruitment process which emphasised the psychological processing of trauma. In order to examine this possibility, a final study involved priming healthy volunteers to reflect on either a neutral life event or a negative, uncontrollable life event, prior to carrying out the scenario task described above. The results revealed that priming with a negative event did not induce a more self-referent CF style. Indeed, it had the opposite effect, indicating that such priming is unlikely to be a significant factor in the pattern of results in the trauma survivors. This set of studies indicates that the experience of a traumatic life event, regardless of whether or not that event leads the victim to develop PTSD, seems to result in a CF reasoning style that emphasises the upward mutation of self-referent behaviour, even for non-autobiographical events where changes in the person's behaviour could not reasonably have made any difference at the time. This is consistent with upward, self-referent CF reasoning having the cognitive function of reinforcing a sense of self-control following the experience of trauma

Project CE6: Neuropsychological deficits in recognition, perception and experience of emotion

Scientific Direction: Calder (40%), Dalgleish (25%), Lawrence (30%).

Research support: Golden (20%), Keane (40%).

MRC-supported students: Croucher (1 yr, 100%).

Project CE2 addressed the perceptual processing (i.e., front-end encoding, configural processing, etc.) of facial expressions. A full understanding of facial expression recognition requires an appreciation of the mechanisms underlying the identification of the emotions displayed (i.e., that a facial expression signals fear, rather than anger or disgust, etc.). Calder has addressed this by studying different patient populations. In earlier research, Calder and collaborators found initial evidence that the recognition of facial signals of fear and disgust may be supported by separate neural systems (Calder, Young, Rowland, Perrett, Hodges, et al, 1996b; Sprengelmeyer, Young, Calder, Karnat, Lange, et al, 1996). Bilateral amygdala lesions were found to impact primarily on the recognition of fear, and to a lesser extent anger, (Calder et al., 1996b) whereas patients with Huntington's disease showed a disproportionate impairment in recognising facial expressions of disgust (Sprengelmeyer et al., 1996). Project CE6 has built on these findings, characterising more completely the functional and neurological dissociation between fear and disgust processing. In addition, work with Lawrence has addressed the neural underpinnings of anger processing. These findings have important theoretical implications and are reviewed in a recent Nature Reviews Neuroscience article by Calder, Lawrence, & Young (2001b). The research addresses a longstanding debate concerning whether the representation of emotion involves individual systems for separate emotions, or an integrated system for all emotions (Calder et al., 2001b). More specifically, the research provides insights into the neural mechanisms underlying the recognition of individual emotions, and highlights parallels between human and comparative research (LeDoux, 2000; Garcia, Forthman Quick, & White, 1983). On the basis of these findings we have proposed that an effective approach to the neuropsychology of human emotion is to use phylogenetic data to guide a search for dissociable emotional systems.

CE6.1 A cross-modal system for recognising fear

Calder's collaborative neuropsychological projects have confirmed the amygdala's role in processing facial expressions of emotion, and in particular fear (Adolphs et al., 1999; Broks et al., 1998). In collaboration with Scott (University College London), Calder has addressed the contribution of the amygdala to the recognition of emotion from vocal cues (Scott et al., 1997) in a case study of DR, a lady with selective bilateral amygdala damage who shows impaired recognition of fear and anger (Calder et al., 1996b) from the face. DR showed an identical pattern in the vocal domain, supporting the view that the amygdala contributes to the recognition of these emotions across different sensory modalities (Calder et al., 2001b). This proposal is also supported by collaborative functional imaging (fMRI) projects with Phillips, and Morris and Dolan, which showed enhanced amygdala signals for facial (Phillips et al., 1998; Phillips et al., 1997; Morris et al., 1998) and vocal (Phillips et al., 1998) signals of fear. These observations lend support to Calder et al.'s (2001b) proposal that fear recognition is achieved by a mechanism that codes emotional information from multiple sensory modalities.

CE6.2 A dissociation between fear recognition and memory for negatively-valenced material

Recent functional imaging and patient-based research has implicated the amygdala in enhanced memory for negatively-valenced material. In collaborative work (Papps, Calder, Young, & O'Carroll, in press), Calder has investigated memory for emotional material in DR (see CE6.1; Calder et al., 1996; Scott, et al., 1997). DR showed intact memory for negatively valenced pictures and words, providing the first evidence that memory and recognition of negative material rely on dissociable systems. These findings were attributed to the fact that DR's amygdala damage is incomplete.

CE6.3 Disgust recognition in OCD and Tourette's syndrome

Calder's collaborative work with Sprengelmeyer has demonstrated that Huntington's disease (an autosomal dominant neurogenetic disorder that, in its early stages, particularly affects the basal ganglia) causes disproportionate impairments in recognising facial expressions of disgust (Sprengelmeyer, 1997). To further investigate the role of the basal ganglia in disgust processing, Sprengelmeyer and Calder (Sprengelmeyer et al., 1997b) examined two psychiatric disorders associated with abnormal metabolic activity in this brain region, obsessive compulsive disorder (OCD) and Gilles de la Tourette syndrome (Braun et al., 1995; Rapoport, 1989; Rapoport & Fiske, 1998). The results showed that the OCD group and a sub-group of the Tourette's participants with co-morbid OCD symptoms showed a selective impairment in recognising disgust facial expressions. One interpretation is that these findings emphasise the role of the basal ganglia in recognising disgust. In addition, it was proposed that the presence of OCD symptoms in the patients' childhood years may have led to a weakened mapping between self-experienced emotion and the facial expressions of others.

CE6.4 Functional imaging studies of disgust processing

Huntington's disease, OCD and Tourette's syndrome are not characterised by focal neuropathology. Hence, although these patient-based studies point towards the probable involvement of the basal ganglia in disgust, the evidence is indirect. In this respect functional imaging research has been particularly informative. Using stimuli developed from program CE2, Calder's collaborative work with Phillips (Phillips et al., 1998; Phillips et al., 1997) has identified two areas involved in processing facial expressions of disgust - the insula and the basal ganglia. Insula involvement is particularly interesting given its role in gustatory function (Augustine, 1996; Small et al., 1999). Of equal relevance is research showing that lesions to the insula or pallidum of rats interfere with conditioned taste aversion (Dunn & Everitt, 1988; Hernadi, Zaradi, Faludi, & Lenard, 1997). Together these findings concur with the theory that disgust has developed from a more primitive system involved in distaste (Rozin & Fallon, 1987; Rozin, Lowery, & Ebert, 1994).

CE6.5 A cross-modal system for recognising disgust

While functional imaging of healthy participants identifies brain regions that are correlated with certain behavioural tasks, it provides no information about whether these regions are necessary and sufficient for successful performance of these tasks. Hence, it is important that Calder has provided further evidence for the role of the insula/basal ganglia regions in processing disgust in the form of a case study of a man (NK) with a focal lesion affecting these areas (Calder, Keane, Manes, Antoun, & Young, 2000b). NK's damage is lateralised to the left and includes the insula, putamen, internal capsule, globus pallidus, and the head of the caudate. NK showed highly selective impairments in recognising disgust from facial and vocal cues, and in his self-reported experience of this emotion. NK's results are consistent with damage to a system that is involved in the recognition of disgust from different modalities, and in the experience of disgust (Calder et al., 2001b).

CE6.6 Differential effects of ageing on the recognition of fear and disgust

In line with the proposal that separate neural systems underlie the recognition of fear and disgust, Calder and Manly have shown differential effects of ageing on the recognition of these emotions (Calder et al., in press). On two tests of facial expression recognition with five age groups ranging from 20 years to 70 years, increasing age produced a progressive reduction in the recognition of fear and, to a lesser extent, anger. In contrast, older participants showed absolutely no reduction in recognition of facial expressions of disgust; rather, there was evidence of an improvement. Recognition of other facial expressions showed no significant evidence of deterioration (or enhancement) across age groups. These results are consistent with the differential effects of ageing on two brain regions underlying the recognition of, respectively, fear and disgust. In relation to fear, research has shown that medial temporal pathology (including the amygdala) is a consequence of normal ageing (Anderton, 1997), while fMRI research has demonstrated reduced amygdala activation to negative facial expressions with increasing age (Iidaka et al., 2001). In contrast, the gross structure and neurochemistry of the pallidum, a region of the basal ganglia implicated in fMRI studies of disgust (Phillips, et al. 1997; Phillips, et al. 1998) and taste aversion (Hernadi et al., 1997), is largely spared by ageing (Raz, 2000).

CE6.7 The contribution of frontal systems to facial expression recognition

The work discussed above identified separate neural mechanisms involved in processing fear (amygdala) and disgust (insula and basal ganglia). Other studies have emphasised the important role of the frontal lobes in processing emotional cues in general, and some have suggested that the systems involved in coding individual emotions may feed into more general emotion systems in frontal cortex (Sprengelmeyer, Rausch, Eysel, & Przuntek, 1998). If this is correct, then we would expect to see general emotion recognition impairments following frontal cortex damage. Keane, Calder, Hodges and Young (2002) investigated this issue in a series of patients with frontal variant frontotemporal dementia (fvFTD), a condition that largely affects the frontal regions of the brain but particularly the ventromedial frontal lobes. Results showed that fvFTD was associated with impaired recognition of a number of emotions from both facial and auditory cues. In contrast, there was no evidence of impaired recognition of identity from faces. These results emphasise a role for the frontal lobes in processing emotional cues from different sensory modalities. In addition, they suggest that previous reports of impaired facial expression recognition in the absence of impaired facial identity recognition, may have been incorrect to interpret this pattern as the antithesis of prosopagnosia (impaired facial identity recognition). Rather, as suggested by the results of the fvFTD study, this pattern may instead reflect impaired recognition of emotion.

CE6.8 Perceptual and motor codes involved in facial expression recognition

It is tempting to think of the perceptual mechanisms underlying facial expression recognition as analogous to those for facial identity. However, we should be cautious in adopting this view because we not only recognise expressions in other people's faces, we generate them ourselves. Hence, the mental representation of facial expressions has the added requirement of a motor-program code (to describe how to produce the expression) in addition to a visual code. The extent to which these two codes interact is unclear. To investigate this issue, Calder studied a group of subjects with a rare congenital disorder that causes facial diplegia (Möbius Syndrome) (Calder, Keane, Cole, Campbell, & Young, 2000a), meaning that they have never produced normal facial expressions. Anecdotal reports had suggested that this group are severely impaired at recognising facial expressions, but until now, there has been no systematic research. Calder found no evidence of marked deficits in facial expression recognition in the Möbius individuals. These findings suggest that there may be minimal interaction between motor-code and visual representations for facial expression.

CE6.9 Selective deficits in anger recognition

Lawrence and Calder have used data from ethology and ethopharmacology to make and test predictions about selective deficits in emotion recognition. In particular, they argued that certain emotions (fear, disgust, anger) can be linked to processing in defense systems involved in detecting and coordinating flexible responses to different ecological threats. For example, appetitive aggression occurs in the context of resource/dominance disputes in a wide variety of species. Hence, the possibility arises that a specific neural system may have evolved to detect and coordinate responses to this specific form of challenge or threat. The dopamine system has been implicated in the processing of signals of aggression in social-agonistic encounters in several species. Acute administration of the dopamine D2-class receptor antagonist sulpiride was used to induce dopaminergic antagonism in healthy male volunteers. This produced a selective disruption in the recognition of facial expressions of anger (signals of appetitive aggression in humans), in the absence of impairment to other emotions (e.g. fear, disgust) or to facial identitiy processing (Lawrence, Calder, McGowan, & Grasby., 2002). These results provide strong support for evolutionary approaches to emotion, but are difficult to reconcile with approaches based on a limited number of dimensions, such as valence and arousal. Such approaches have difficulty explaining, for example, selective deficits in the processing of anger, but not fear.

CE6.10 Mechanism of psycho-surgery for depression

Patients who suffer from severe, chronic depression that is resistant to the standard interventions of pharmacotherapy and psychological therapy have the option of psychosurgery as a treatment-of-last-resort. Dalgleish and Teasdale, in collaboration with colleagues at the Institute of Psychiatry, investigated a group of patients who had undergone Stereotactic Subcaudate Tractotomy (SST) as anti-depressant neurosurgery. Typically SST leads to remission/recovery from depression in 60% of patients. However, it is unclear what the psychological mechanisms associated with this anti-depressant effect are, nor whether there are secondary cognitive/neuropsychological costs associated with the operation.

In order to address these two questions, patients who had recovered from depression following SST (SST-recovered) were compared to patients for whom the operation had not been successful (SST-depressed) on a broad range of cognitive and neuropsychological measures (Dalgleish, Yiend et al., submitted). The results revealed that the SST-recovered patients were insensitive to negative feedback information on a widely used decision making task (Bechara, Damasio, Damasio, & Anderson, 1994) relative to the SST-depressed group. However, there were no other differences between the groups on a broad neuropsychological test battery indexing language, general intelligence, attention, memory and executive functioning. The data were re-examined in a correlational analysis and it was also found that the degree of recovery from depression following SST, as indexed by depression self-report measures, was associated with increased insensitivity to negative information.

In order to investigate which group was performing normally, a sample of matched, never-depressed controls completed the task. The performance of the controls did not differ from that of the SST-depressed group but was significantly different to that of the SST-recovered sample, with the recovered sample showing greater insensitivity to negative feedback relative to the healthy, never-depressed individuals.

It remained possible that the performance of the SST-recovered patients was a function of recovery from depression per se rather than a function of recovery following psychosurgery. In order to examine this possibility, patients who had recovered from depression with medication alone (medication-recovered) also completed the task. Again the results revealed significantly augmented insensitivity to punishment in the SST-recovered group and the medication-recovered participants were no different to the healthy controls and SST-depressed samples.

This pattern of results suggests that SST for depression may work by inducing a relatively enhanced insensitivity to negative information. Such insensitivity would potentially disrupt the vicious cycles of processing of negative information that are seen as central to the maintenance of the disorder in the theoretical models developed in the Cognition and Emotion group (Power & Dalgleish, 1997; Teasdale & Barnard, 1993). The results also indicate that the anti-depressant effect generated by SST does not seem to be at the expense of a more general deficit in neuropsychological functioning as measured by a standard test battery. This is important clinical information for those who are contemplating this irreversible treatment-of-last-resort.

Project CE7: Attention and the manipulation of affect perpetuating processes

Scientific Direction: Mathews (45%), Teasdale (25%).

Research support: Green (75%), Yiend, (45%).

MRC-supported students: Hoppitt (I year, 100%), Potts (3 yrs, 100%).

The manipulation of cognitive processes assumed to produce or maintain emotional states and disorders provides an opportunity both to test multi-level analyses of those disorders, and to identify the key processes to be modified in clinical interventions to treat or prevent those disorders. Studies in both anxiety and depression have investigated the effect of attentional manipulations on affect perpetuating processes.

CE7.1 Threat-related biases

CE7.1.1 Manipulation of attentional bias

This project is concerned with the issue of whether emotional processing biases can be manipulated. Establishing such experimental control would allow us to investigate the mechanisms underlying individual differences in these processing operations, their causal relationship with emotional states, and consequently, whether and how this control can inform therapeutic applications. In a first series of experiments in the area, Mathews addressed specific hypotheses about the critical factors underlying individual differences in attention to mild threat cues such as words or pictures. One hypothesis is that these cues are more aversive for anxiety-prone individuals because they have experienced more unpleasant life events associated with them. A second is that, even if there are no such differences in association frequency, anxiety-prone people learn negative associations more readily. The third is that, even if threat cues are no more aversive for anxiety-prone individuals than for others, they are less able to prevent attention capture by these cues.

In a series of experiments, in collaboration with Mackintosh (and Fulcher), Mathews found evidence consistent with this last hypothesis (Fulcher, Mathews, Mackintosh, & Law, 2001). Neutral pictures were paired with neutral, positive or negative captions, while participants formed an image linking the two. After a delay, the negative-paired pictures were rated as less liked, with no differences between groups high or low in negative emotionality. However, in a task in which participants had to find targets superimposed on the pictures, the group with high negative emotionality were slowed by negative-paired pictures, while the low group was slowed more by positive paired pictures. These data suggest that, even when matched for emotional learning, new negative cues capture attentional resources more in those prone to negative emotions.

In a further study of this kind, Mackintosh & Mathews (in press) used a spatial cueing task to contrast attention to mildly emotionalised cues with that to more severely threatening pictures. In a non-anxious group there was a general tendency for attention to the more mild cues to be actively avoided, although the more severe pictures typically held attention. This provides support for the view that non-anxious individuals can adaptively prevent their attention being captured by mildly emotional cues but this control is overridden in most people as threat severity increases.

CE7.1.2 Evidence that biased processing has causal effects on mood

Although Mathews and colleagues have postulated that attentional and interpretative biases play a central role in the self-perpetuating patterns of information processing in anxiety disorders, until recently there has been no convincing evidence that this relationship was causal. Recently, however, techniques have been developed for inducing emotional processing biases in the laboratory, and have been used to reveal the conditions under which they can cause changes in vulnerability to anxiety.

In an initial series of experiments (Grey & Mathews, 2000) volunteers were presented with threat/neutral homographs as clues to solve word fragments (e.g. batter – in-ury or batter - pa-cake), or in the context of relationship judgements (e.g. Injury - batter. Related?). Participants were randomly allocated to decisions involving either threatening or neutral meanings of homographs, and then tested with new homographs not previously exposed. Both when tested with similar decisions as used in earlier, and with a completely new lexical decision task, these participants showed evidence that their prior experience continued to influence their interpretation of new homograph meanings. Most critically, in current experiments (in collaboration with Colin MacLeod), Mathews has shown that subsequent exposure to an ambiguously threatening event (videos of accidents) leads to different emotional consequences. Those exposed to negative homograph meanings reported increases in state anxiety, while those exposed to benign meanings did not. Post - experimental interviews indicated that participants were unaware of any connection between their prior exposure and later anxiety reactions.

In a parallel series of experiments, Mathews & Mackintosh (2000) have used more complex descriptions of real-life events, having threatening or benign outcomes determined by a final word. In some experiments, volunteers simply read these descriptions while imagining themselves in the situations, while in others they read the same passages up until the final word, which was presented in a to-be-completed fragment form. In all experiments, participants were randomly allocated to threatening or benign outcomes, and then read a new set of descriptions with ambiguous outcomes. Their interpretation of these ambiguous events was established indirectly using a recognition test involving negative and positive versions of the original items. This procedure has revealed a very robust interpretative bias that lasts at least into the following day. Another critical finding was that anxiety changed in a congruent direction when (and only when) training involved participants in the active generation of emotional meanings (e.g. by resolving the final word fragment).

In reviewing these (and other experiments on training attention), Mathews & MacLeod (2002) concluded that experimental induction of processing biases can readily be achieved in the laboratory, without the awareness of participants. The induction procedures themselves do not normally induce emotional changes directly (with some predictable exceptions), but do influence how later events are interpreted. When these interpretations have emotional implications for the individual concerned, they elicit congruent changes in mood. These findings thus provide the first evidence that processing biases can indeed be a cause of anxiety, albeit indirectly by influencing how new events are interpreted.

CE7.2 Modes of self-attention

Teasdale (1999c) drew attention to the apparently anomalous relationship of self-attention to the perpetuation and amelioration of emotional disorders. On the one hand, a tendency to focus attention on the self has been consistently associated with emotional disorders, particularly depression. On the other hand, interventions that involve individuals intentionally focusing attention on aspects of emotional experience lead to reductions in disordered emotion. Using the Interacting Cognitive Subsystems (ICS) theoretical framework, Teasdale suggested that this anomaly could be resolved by recognising the existence of different modes of self-focus. These modes are characterised by distinct configurations of processing resources (see project CE3), and, for that reason, are also characterised by distinct relationships to the perpetuation of emotion. The ICS analysis (Teasdale, 1999c) suggested that perpetuation of depression involves a ruminative mode of self-attention, focused on processing discrepancies between conceptual-level (propositional) representations of current and goal self-states. This analytical mode involves thinking about the self as a conceptual object. Conversely, therapeutic change involves a mode of self-focus controlled at a more schematic (implicational) level. This experiential mode involves less goal-related discrepancy processing. In this mode the subjective self is experienced directly as feelings, thoughts, and body sensations in the moment. Teasdale and colleagues have developed methods to induce experimentally these two modes of self-focus and have demonstrated differences in their effects on aspects of autobiographical memory.

CE7.2.1 Effects on overgeneral autobiographical memory in clinical depression

Measures of overgeneral autobiographical memory (OGM) (see CE5) predict the course of depressive disorders, and, for that reason, OGM has been assumed to reflect processes central to the maintenance of depression. Because OGM is shown by both acutely depressed and recovered patients, and is unrelated to the severity of depressed mood, it has been assumed to be a persistent, trait-like characteristic of depression-prone individuals. However, in collaborative experimental work Teasdale has shown, for the first time, that OGM in both depressed adults and children can be modified by manipulations of attentional focus as brief as 8 minutes (Park, Goodyer & Teasdale, submitted; Watkins, Teasdale & Williams, 2000; Watkins & Teasdale, 2001; Watkins & Teasdale, submitted). These findings suggest that the apparent stability of OGM in the depression-prone reflects its dynamic maintenance by processes that can be disrupted by competing tasks, rather than the trait-like characteristic, previously assumed. Further, these studies have identified the interruption of analytical, ruminative thinking as a feature of interventions that reduce OGM. From their findings, Watkins and Teasdale (2001) proposed that OGM reflects chronic ruminative attempts to analyse and understand current and past difficulties.

These studies of brief attentional manipulations in clinically depressed individuals have also provided an opportunity to examine the effects of analytical versus experiential self-focus on OGM, a variable known to be related to the maintenance of depression. Watkins and Teasdale (2001) induced analytical and experiential self

- focus in clinically depressed individuals. The inductions had similar effects on depressed mood, but experiential self-focus significantly reduced the overgenerality of memories, compared to analytical self - focus. In a subsequent study (Watkins & Teasdale, submitted) in which the analytical and experiential inductions used identical items and differed only in the instructional set within which participants processed aspects of self-experience ("think about" versus "experience directly"), the same pattern of results was obtained. These results are consistent with Teasdale's (1999c) proposals that ruminative self-focus acts to perpetuate depression, whereas experiential self-focus can ameliorate it. The latter suggests that more extended training in experiential self-focus could be a valuable clinical intervention to modify depression. This suggestion is developed further in CE8.

CE7.2.2 Effects on the at-oneness of autobiographical memories

In parallel with the above studies of depressed patients, experiments in non-depressed individuals have examined the effects of ruminative analytical versus experiential self-focus on a novel measure of autobiographical memory. This measure is assumed to reflect affect-related discrepancy-based processing. Within Teasdale's (1999c) analysis, such processing is seen as a characteristic feature of ruminative analytical self-focus. It was assumed that the autobiographical memories most accessible at a given time provide a window into the processing configuration active at that time. Ratings of how "at one with things" individuals felt in their most accessible memories were used as a measure of goal-related discrepancy-based processing: low at-oneness was assumed to reflect high discrepancy processing, characteristic of a ruminative, analytic, form of self-focus. Consistent with this assumption, low ratings of at-oneness of autobiographical memories uniquely and substantially predicted high scores on dispositional ruminative self-focus and neuroticism in a sample of 130 normal volunteers (Teasdale & Green, submitted). Three experiments examined the effects of experimentally induced analytical self-focus versus experiential self-focus on the at-oneness of autobiographical memories. Compared with analytical self-focus, experiential self-focus consistently increased the at-oneness of autobiographical memories, while having no differential effect on the happiness or unhappiness of memories, or on mood. Putting the negative correlation of at-oneness with ruminative self-focus, observed by Teasdale and Green, together with the positive effects of experiential self-awareness on at-oneness observed experimentally, these findings support Teasdale's (1999c) suggestion that analytical self-focus and experiential self-focus are distinct forms of self-attention, with different functional properties. Further, the experimental findings in non-depressed individuals provide further evidence that, relative to analytical self-focus, experiential self-focus reduces a process (self-related discrepancy processing) assumed to maintain depression.

In summary, Project CE7.2 supports a distinction between analytical self-focus and experiential self-focus, and shows that experiential self-focus can reduce processes implicated in the perpetuation and escalation of depression. These studies provide an experimental foundation for the training in mindfulness (a form of experiential awareness) that is a central component of the innovative relapse prevention programme described in Project CE8.

Project CE8: Development and evaluation of clinical therapeutic procedures and processes

Scientific Direction: Teasdale (50%).

Research support: Green (10%).

Self-supported students: Ma (3 years, 100%).

Major depressive disorder is a lifelong, recurring condition. It follows that prevention of relapse and recurrence is a centrally important therapeutic challenge. Teasdale, in collaborative work, funded by external grants, has investigated the outcomes and therapeutic mechanisms of two psychological interventions for relapse prevention in recurrent depression. One, cognitive therapy (CT), is an established treatment. The other, mindfulness-based cognitive therapy, is a radically novel approach developed by Teasdale and colleagues on the foundation of prior experimental and theoretical work.

CE8.1 Cognitive therapy and the prevention of relapse and recurrence in residual depression

Depressed patients treated with antidepressant medication who still show residual symptoms of depression are at high risk of relapse. In a two-centre trial (Paykel, Scott, Teasdale, et al., 1999) 158 such patients were randomised either to continue with medication and clinical management, or, additionally, to receive CT. CT significantly reduced relapse by approximately 40%. This result is very important (and this trial was identified as one of MRC's highlighted achievements for the year 1999) as it is the first trial to show, unambiguously, that CT can reduce relapse, compared to continuing pharmacotherapy, in just those patients for whom it is most relevant. Effects of CT on relapse were not accompanied by reductions in background levels of depressive symptoms, suggesting that CT acted through reducing the escalation of symptoms at times of potential relapse, rather than through a generalised reduction in symptom levels (Scott, Teasdale, et al., 2000).

This trial also provided an opportunity to investigate the processes through which CT prevents relapse. CT explicitly aims to reduce belief in the content of negative thoughts and dysfunctional assumptions. It has been widely assumed that these changes in belief mediate the relapse prevention effects of CT. However, there has been a consistent failure to support this view empirically. By contrast, an ICS analysis (e.g.Teasdale, 1997a) suggests that CT works, not through changing belief in thought content, but through changing patients' way of processing, or relationship to, their negative thoughts and feelings. For example, the existence of two levels of meaning in ICS (CE3) suggests that representations at one level of meaning can concurrently be the topic of representations at the other level of meaning. This has particular advantages in analysing the role of metacognitive processing in the maintenance and modification of mood disorders (Teasdale, 1999b).

Teasdale's (1997a, 1997b) analysis suggested that increased metacognitive awareness (the ability to see negative thoughts and feelings as events in the mind, rather than identifying with them, or regarding them as necessarily true) is an important aspect of the shift in relationship to negative thinking effected by CT. To test this hypothesis, a memory-based measure of metacognitive awareness was developed and included in the above trial. Consistent with the hypothesis that CT prevented relapse through increasing metacognitive awareness, low metacognitive awareness predicted subsequent relapse, and CT significantly increased metacognitive awareness (Teasdale et al., 2002).

More detailed mediational analyses in this trial (Teasdale et al., 2001) provided further support for the view that CT prevents relapse by changing the way that depressive thinking is processed, rather than by changing belief in its content. First, CT significantly reduced measures of the form of thinking (the extent to which it was absolutistic or "black and white"); second, these measures predicted relapse; and third, the effects of CT on relapse could be accounted for by changes in these measures. By contrast, as in previous studies, measures of belief in the content of negative thinking failed to provide any evidence that changes in belief mediated therapeutic effects. This is the first time that effects of CT in preventing relapse in depression have been shown to be mediated by changes in any cognitive variable. It is particularly important, therefore, that mediation was demonstrated for a measure related to the way that thinking was processed, rather than its content.

This mediational analysis suggested that CT prevents relapse by teaching patients, in depressed mood, to switch out of an habitual ruminative mode of negative thinking into an intentional processing mode in which initial, dysfunctional, "automatic" cognitive products are reappraised using controlled processing resources. In quite separate work (conducted under CE5 but reported here), Sheppard and Teasdale (2000, submitted), using decision latency measures in novel experimental paradigms, independently identified a deficit in such metacognitive monitoring as a feature of acute major depression. Further, they showed that recovery normally involves a transition through a phase in which dysfunctional schematic products are effortfully re-appraised to produce more functional products, before more automatic access to functional schemas is established with full remission. These findings suggest that CT may be effective because it operates through reinforcing the use of a pre-existing meta-cognitive strategy.

In summary, this trial of CT for residual depression provided very important evidence for the clinical efficacy of CT in reducing relapse. It also provided the first peer-reviewed evidence demonstrating the mechanisms through which CT achieves these preventive effects. This evidence supported Teasdale and colleagues' proposals, derived from ICS, that CT works by changing the way in which negative thoughts are processed, rather than through changing belief in thought content. These proposals were the basis from which the novel preventive programme described in CE8 was derived.

CE8.2 Mindfulness-based cognitive therapy for prevention of relapse in recurrent depression

The differential activation analysis of vulnerability to relapse (CE5.1.3) suggests that prevention of relapse and recurrence in major depression requires that patients, particularly those who have experienced multiple episodes, learn how to prevent the escalation of negative, ruminative, thought patterns reactivated by dysphoria. In an analysis of the effectiveness of CT, Teasdale, Segal & Williams (1995) proposed that CT, although explicitly targeted on changing belief in depressive thoughts and assumptions, implicitly teaches patients to prevent escalation of rumination in dysphoria by switching to an intentional processing mode in which negative thoughts and feelings are treated as passing events in the mind, rather than as self or as accurate readouts on reality. The evidence in CE8.1 supports this analysis.

Mindfulness-based cognitive therapy (MBCT) (Segal, Williams, & Teasdale, 2002; Teasdale, 2000) is a radically novel, highly cost-efficient intervention, explicitly designed by Teasdale, Segal and Williams to teach recovered recurrently depressed patients the response prevention skills that the above analysis suggests are necessary, and that are taught, implicitly, by CT. Unlike CT, MBCT does not focus on changing belief in the content of negative thoughts. Instead, it teaches patients skills that allow them to intentionally disengage from negative, ruminative thought patterns reactivated by dysphoric mood at times of potential relapse. MBCT does this by training patients to bring experiential self-awareness (mindfulness) (CE7.2) to their thoughts, feelings and bodily sensations. In parallel, MBCT cultivates metacognitive awareness, the capacity to relate to thoughts and feelings as mental events.

In a three-centre clinical trial, 145 recovered recurrently depressed patients were randomised either to continue with treatment-as-usual or, additionally, to participate in the MBCT programme (Teasdale et al., 2000). For patients with 3 or more previous episodes of depression (77% of sample), MBCT significantly reduced relapse from 66% to 37%. For patients with only two episodes (23% of sample) MBCT was of no benefit. MBCT also increased metacognitive awareness (Teasdale et al., 2002), and reduced overgeneral autobiographical memory (Williams, Teasdale, Segal & Soulsby, 2000). This trial was the first demonstration that a group psychological intervention, administered in recovery, could significantly reduce relapse and recurrence in major depression. It was also the first multi-centre trial of a mindfulness-based clinical intervention.

A subsequent clinical trial (Ma & Teasdale, submitted) with the same design, replicated the finding that MBCT is a highly cost-efficient approach to preventing relapse in patients with 3 or more episodes: relapses were reduced from 78% to 36% for an average therapist contact of only 2 to 3 hours per patient. Again, patients with only two previous episodes failed to benefit from MBCT. This trial provided evidence to support the hypotheses (Teasdale et al., 2000) 1) that MBCT is specifically effective in reducing relapses triggered by dysphoria reactivating autonomous ruminative thought patterns, rather than those provoked by major life events, and 2) that this is the reason why MBCT is ineffective with patients with only 2 episodes; for these patients, relapse was primarily provoked by major life events. MBCT was also found to reduce measures of rumination, thought suppression, and salivary cortisol, compared to the control condition. A therapist manual describing the development, delivery, and evaluation of MBCT has been published (Segal, Williams, & Teasdale, 2002), and a scale to assess therapist adherence to MBCT has been developed and validated (Segal, Teasdale, Williams & Gemar, 2002).

MBCT has attracted wide attention internationally. For example, in 2001, Teasdale was invited by the US National Institute of Mental Health, as the only non-North American participant, to make a presentation on MBCT to an invited working group reviewing approaches to relapse prevention in major depression. In contrast to conventional CT, MBCT makes no attempt to teach patients to address belief in the content of negative thoughts. Instead, it trains patients to access a mode of intentional cognitive processing in which negative thoughts, feelings, and body sensations are regarded as passing objects of attention. The success of this programme in preventing relapse in recurrent depression supports this shift in therapeutic strategy, and opens up new directions for the development of therapeutic procedures that are complementary to existing cognitive therapy approaches across a wide range of disorders. This success also supports the general strategy, inherent in the Cognition and Emotion group, of basing therapeutic interventions on empirically grounded theoretical analyses of emotional disorders and their treatment.

AWARDS AND HONOURS

Dr P. Barnard was appointed to a Visiting Professorship in the Departments of Psychology and Computer Science, University College London, from 2002 to 2007. Dr T. Dalgleish received the May Davidson Award from the British Psychological Society in 1999/2000 for early career contribution to clinical psychology. He also became an Honorary Senior Lecturer in psychology at the Institute of Psychiatry in 1999, and holds a non-stipendiary research fellowship, at Clare Hall College, Cambridge from 1999 to 2002. Dr A. Mathews was appointed to a Visiting Professorship at the Institute of Psychiatry from 1997 onwards. Dr J. Teasdale was elected Fellow of both the British Academy and the Academy of Medical Sciences in 2000.

PUBLICATIONS

(Note: Some papers are included that were published prior to 1998. These represent relevant work that appeared during the interval between the last formal Unit Review and the current reporting period.)

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TRANSFER TO HEALTH SERVICE

The trials demonstrating the efficacy of mindfulness-based cognitive therapy (MBCT) carried out by Dr Teasdale and colleagues have led to the establishment of some MBCT programmes in the NHS.

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4. LANGUAGE AND COMMUNICATION PROGRESS REPORT

Overview

The ability to use and understand language is one of the fundamental human capacities. The scientific understanding of language function requires an interdisciplinary enterprise that combines psychological, linguistic, neuropsychological, neurobiological, and computational inputs. The aim of the Language and Communication programme is to study human language in these terms, as a cognitive, computational, and neural system. Within this global programme, we identified four major research themes. These are summarised below, and presented in more detail in the main body of the report.

More generally, the period under review has been one of development, recruitment, and bedding-down. In particular, we have successfully instigated a shift of emphasis towards understanding the neural basis of language processing. The appointment of a senior EEG and MEG specialist (Pulvermüller) and an fMRI specialist (Johnsrude) in the year 2000, has resulted in a vigorous and successful neuro-imaging programme, which, despite only being fully operational for the last 18 months, has already begun to yield valuable new results. These more recent developments have interacted strongly with the behavioural aspects of the programme (led by Marslen-Wilson and by Norris) which have been running for the full period under review. These cross-programme interactions are a major source for the proposals we will make for next quinquennium.

Project L1: Phonological and lexical processing of speech

The focus of this project is on the key early processes in understanding spoken language. We investigate the nature of the transformation undergone by the speech input as it is mapped from early auditory analysis through to representations of phonological form and subsequent access to the mental lexicon. These questions are explored in an interdisciplinary framework, following three main strands.

• A major subcomponent of the project uses fMRI neuro-imaging techniques to probe the brain systems involved in speech analysis. This work looks both at general properties of auditory analysis at the cortical level, and at those systems specifically engaged by speech. Important collaborative work with other groups in Cambridge (Roy Patterson's group in Physiology) and with the MRC IHR in Nottingham and the FIL in London have begun to map out the very specific functional differentiation of cortical areas in and around primary auditory cortex.

• A second component takes a more cognitive and computational approach, examining the role of phonological and lexical factors in the processes of speech segmentation – how the stream of speech is segmented into phonemes, syllables and words. There are two key findings here – the identification of the "Possible Word Constraint", a new language universal principle of speech segmentation, and the demonstration, for the first time, of clear-cut effects of acoustic-phonetic cues in disambiguating onset-embedded words (e.g. cap in captain) that were previously thought to present intractable problems for several classes of word-recognition models.

• The third component continues the development of two leading theories of spoken word-recognition. The Cohort model, long associated with Marslen-Wilson, has evolved into a distributed, connectionist format, with a novel processing architecture which makes distinctive predictions about the role of semantic factors in the word-recognition process. The Shortlist and Merge models, developed by Norris and colleagues, presents new research and theoretical developments clarifying the role of feedback in word recognition and in perceptual adaptation to speech distortions. In a complementary development, we have initiated pioneering neuro-imaging research, using variations in speech intelligibility to map out brain regions involved in mapping from sound to meaning, and potential interactions between them.

Project L2: The structure of lexical representation

The second main project focuses on words, in the mind and in the brain. The form and meaning of words play a critical role in language comprehension and production. We examine here the properties of the mental lexicon – the mental representations of knowledge of words – from cross-linguistic and neuro-psychological perspectives.

• A scientific account of the mental lexicon requires comparisons across languages. Over the last quinquennium we have been able to develop an unique set of systematic empirical comparisons, adding two new language families (represented by Polish and Arabic) to previous studies of Chinese and of French and Italian. This not only reveals a surprising degree of divergence in organising principles across languages, but also documents new morphological phenomena – for example, the highly abstract prosodic morphemes that dominate word formation in Arabic.

• The second major project here takes forward the highly visible debate on the significance of regular and irregular morphology ("words" vs "rules") in the English past tense. In influential work, carried out in collaboration with Tyler (Cambridge), we have amassed considerable new evidence for a neuropsychological double dissociation between the processing of regular and irregular past tense forms in aphasic patients. Further work using behavioural and neuro-imaging (EEG, fMRI) techniques with intact adults, points to a re-interpretation of the regular/irregular contrast in English as primarily morpho-phonological in nature – a conclusion which is supported by further cross-linguistic studies of regularity and irregularity in French and Polish.

Project L3 / M4: Short-term memory and speech perception

This third project, joint with the Memory Group, seeks to unite the study of short-term memory (STM) and the study of language comprehension. Speech recognition and comprehension are reliant on temporary storage, and this requires an understanding of the systems involved in the representation and storage of ordered information in STM. Our emphasis here was on computational modelling, supported by empirical work to place additional constraints on theoretical development.

• The key achievement here was the development of a new model of the phonological store component of working memory. This model (the Primacy model) gives a complete and precise account of the fundamental behavioural characteristics of serial recall from STM. An extensive presentation of this model was published in the leading journal in the field.

• The second important aspect of the project was the acquisition of new data that allowed the rejection of popular alternative explanations of STM based on associative chaining or on position-item correspondences.

Project L4: Neurophysiology of language

A priority for this quinquennium was to add the temporal precision provided by EEG-based neuro-imaging to the spatial precision provided by fMRI and PET. By the end of 2000, a new EEG laboratory was built and equipped, and a senior EEG specialist (Pulvermüller) and his team were installed at the CBU. Pulvermüller also brought with him a fruitful collaboration with Ilmoniemi's MEG lab in Helsinki, giving us access to this important new technology. Working within a theoretical framework based on Hebbian concepts of distributed, functionally connected ensembles of neurons, the group is making significant advances in several directions. We highlight two of these here.

• The existence of category-specific brain processes has been a salient issue in recent cognitive neuroscience, and is predicted by Hebbian correlation learning. A series of EEG studies have shown neurophysiological differences between word categories, with, for example, action-words related to different motor areas (e.g. hand vs mouth, as in pick vs lick), showing differential cortical activation in the predicted frontal motor areas. Neuropsychological lesion studies have provided confirmatory results, and preliminary data from MEG and TMS are also encouraging.

• Mismatch Negativity (MMN), a neurophysiological response that reflects automatic cortical processes, has been found in recent EEG and MEG studies to be sensitive to higher-order linguistically related processes. Words elicit a stronger MMN than meaningless pseudowords, and the stems of content words and inflectional affixes elicit MMN's with different latencies and topographies. Striking recent results suggest that MMN responses directly reflect the timing of cortical events linked to word recognition processes at different sites in perisylvian cortex.

Project L1: Phonological and lexical processing of speech

Scientific direction: Norris (50%), Marslen-Wilson (20%), Johnsrude (95%), Gaskell (100%)

MRC-scientists: Davis (80%)

MRC research support: Butterfield (100%), Woods (50%), van Casteren (25%)

The focus of this project is on how the phonetic and phonological properties of language are represented and accessed in the adult system. What is the nature of the transformation undergone by the speech input as it is mapped from early auditory analysis through to lexical representations of phonological form and the generation of phonological perceptual experience? This is explored in an interdisciplinary framework, following three main strands.

Subproject L1.1 employs neuro-imaging techniques in a series of experiments that probe the brain systems involved in speech analysis. This work looks both at general properties of auditory analysis at the cortical level, and at those systems specifically engaged by speech. This was collaborative work with Hall (MRC IHR, Nottingham), Griffiths (FIL, London) and with Patterson and Uppenkamp of the Centre for the Neural Basis of Hearing (CNBH) in the University of Cambridge Department of Physiology. Subproject L1.2 takes a more cognitive and computational approach, examining the role of phonological and lexical factors in the processes of speech segmentation – how the stream of speech is segmented into phonemes and into higher-order syllabic and morphemic units. The third subproject, L1.3, develops contrasting approaches to the functional architecture of the word recognition system, contrasting current versions of the Cohort model (Gaskell, Marslen-Wilson) with the Shortlist and Merge models (Norris). This also includes recent neuro-imaging research, using variations in speech intelligibility to map out brain regions involved in mapping from sound to meaning, and potential interactions between them (Johnsrude, Davis).

L1.1. Imaging auditory cortex: from sound to phonology

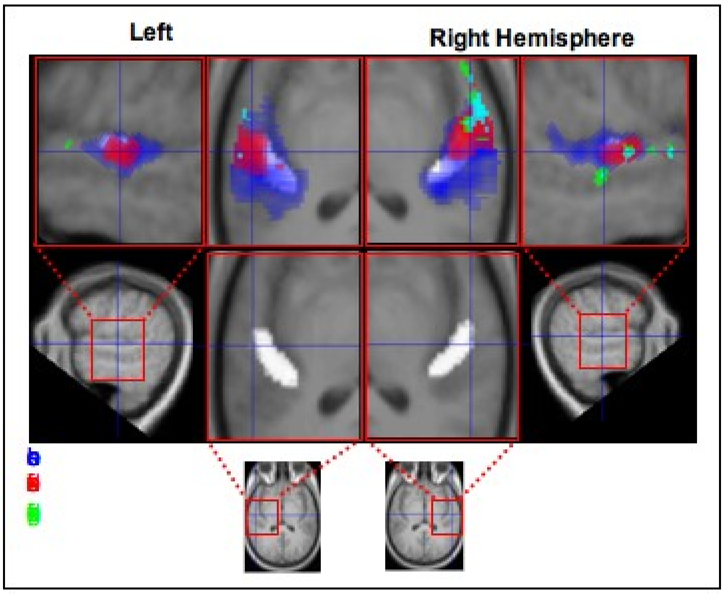
The anatomical organization of the auditory system and its onward connections provides a framework within which to explore the functional organization of speech perception. The anatomy suggests several parallel streams of processing extending hierarchically outwards from primary auditory cortical core (on Heschl's gyrus), through belt and parabelt nonprimary auditory areas. Although the anatomy of these areas in humans is still uncertain, they can be expected to be hierarchically organized and functionally differentiable, as they are in macaques (see Rauschecker, 1998; Kaas & Hackett, 2000, for reviews). In preliminary, collaborative examination of the functional properties of these systems, projects L1.1.1 – 3 investigate the general analytic capacities of the auditory system such as pitch extraction, temporal processing, sound localization and auditory grouping. Project L1.1.4 focuses on the transition from the processing of sound to the processing of speech.

L.1.1.1. Pitch based on temporal cues

Pitch extraction is critical for the tracking of prosodic contour (fundamental frequency) in fluent speech. A potential complication in searching for the neural basis of pitch perception is that two separate pitch mechanisms may be involved. The periodic portions of speech, such as vowels, can be described as spectrally shaped harmonic complexes. The lower harmonics of such sounds are resolved by the peripheral auditory

system, and changes in their fundamental frequency ("F0", corresponding to the perceived pitch) could be encoded either by changes in the temporal response ("phase locking") of auditory nerve fibres to individual harmonics, and/or by changes in the place of excitation along the basilar membrane. It is also possible to produce a tone with a strong pitch by regularizing the time intervals in a broadband noise, so that one time interval (a few ms) occurs more often than any of the others. When high-pass filtered at frequencies of 500 Hz or above, these regular-interval (RI) sounds (Patterson, 1994) effectively excite all frequency channels in the same way as random noise, with no resolved spectral peaks. The perception of pitch elicited by these stimuli must therefore rely on extraction of regular time intervals of a few ms, rather than extraction of any prominent spectral features, enabling one to test temporal models of pitch perception (eg, Patterson et al., 1994).
Together with colleagues from the CNBH and the FIL, Johnsrude has investigated this issue in a series of fMRI studies (Griffiths, Uppenkamp, Johnsrude, Josephs & Patterson, 2001; Patterson, Uppenkamp, Johnsrude & Griffiths, in press). Listeners were presented with random noise bursts, a series of RI sounds with a fixed pitch, and a series of RI sounds with a pitch excursion between successive items. Sounds with a pitch generated greater activation than did the random noise within a confined region on lateral Heschl's gyrus (HG), in a probable auditory belt area. Relative to the fixed-pitch stimuli, the melodic pitch sequence generated a greater response at the lateral-most extremity of HG and on the convexity of the superior temporal gyrus (STG) in the right hemisphere; see Figure L.1. These results confirm that non-primary auditory cortex is important for the analysis of spectrotemporal patterns in sound. Furthermore, the centre of activity shifts anterolaterally into higher-order areas as information must be integrated over time.

Figure L.1 : fMRI response to RI sounds in auditory regions: The top panels show activation on the supratemporal plane: activation data is superimposed on a mean structural image from 9 subjects. The white area in the central panels denotes the average location of Heschl's gyrus as identified using morphological criteria in these subjects. Noise, compared to silence, activates a large auditory area bilaterally (shown in blue). Extraction of pitch based on temporal cues activates an area at the lateral edge of Heschl's gyrus in both hemispheres (red): this is probably an auditory belt region. Finally, introduction of a pitch difference between successive tones produces right-dominant activation, at the lateral extremity of Heschl's gyrus, extending anteriorly and posteriorly along the convexity of the superior temporal gyrus (green/aqua). (See Patterson et al., in press)



L1.1.2. Stimulus complexity

Whereas single-frequency tones may activate focal areas within an auditory field, broadband sounds should activate larger neuronal populations, particularly within the non-primary auditory areas that correspond to belt cortex (Rauschecker & Tian, 1995). Using fMRI, we have reported (Gonçalves, Hall, Johnsrude & Haggard, 2001; Hall, Johnsrude, Haggard, Akeroyd, & Summerfield, 2002) activation in putatative core auditory regions to simple tones, with greater activation in non-primary auditory areas (including lateral superior temporal planum bilaterally) when activation to simple tones was subtracted from that to a harmonic-complex tone of the same pitch. Activation was also greater to frequency-modulated tones than to steady-state tones in these areas. Giraud, Lorenzi, Ashburner, Wable, Johnsrude, Frackowiak, & Kleinschmidt (2000) also reported a significant effect of amplitude modulation in bilateral primary and non-primary areas, strongest in the posterolateral regions of the superior temporal gyrus. These results, suggesting that greater stimulus complexity leads to greater responding in nonprimary areas, is consistent with a hierarchical model of auditory processing.

L1.1.3. Localization of activation foci relative to auditory cortex

An important premise of functional imaging is that activation will follow follow anatomy (Brett, Johnsrude, & Owen, 2002): anatomically homologous areas in the two hemispheres, which are presumably similar in function (such as primary auditory cortex) should show similar activation patterns. Given that auditory stimuli generally yield strong, bilateral auditory cortical activations, this assumption can be tested directly, by examining whether the right-left asymmetry evident in the anatomy of primary auditory cortex (PAC) (see Penhune, Zatorre, MacDonald & Evans, 1996; Rademacher, Morosan, Schormann, Schleicher, Werner, Freund, & Zilles, 2001) is also evident in functional data. Under conditions in which primary auditory cortex is assumed to be activated (in comparing sound conditions to silent baseline conditions, for example), one would expect to observe peak activation more anteriorly in the right auditory region than in the left, if activation does respect the anatomical asymmetry. We compared, across 28 published positron emission tomography (PET) studies of audition, activation foci in the right and left auditory region to the centroids (centres of mass) of auditory cortex in the two hemispheres, using either the probability-weighted centroids of Heschl's gyrus; the location of PAC (Penhune et al., 1996) or the probability-weighted centroids of PAC itself (Rademacher et al., 2001). We found that activation foci were consistently farther away from PAC, falling in nonprimary cortex, in the right hemisphere compared to the left. Moreover, across a wide range of stimulus types, activation was consistently more intense in the right hemisphere compared to the left (Johnsrude, Giraud, & Frackowiak, 2002). These findings are hard to reconcile with conventional neuroimaging assumptions, and may be due to vascular artefact and partial volume effects resulting from spatial smoothing. Whatever their origin, the results suggest that the spatial resolution of PET is insufficient to explore the functional organization of auditory core, belt and parabelt regions. FMRI, in part because of its ability to reveal effects within subjects, may be a better way to study auditory functional organization (Owen, Epstein, & Johnsrude, 2002).

In a recent fMRI study (Patterson et al., in press), we compared auditory activation in a group to activation patterns within individual subjects, to determine whether there were consistent differences between individual listeners in the location of functional activation within auditory cortex, and whether the differences corresponded to differences in the sulcal and gyral morphology of individuals (Penhune et al., 1996). After spatial normalization, variability in gross anatomical landmarks (sulci and gyri) from subject to subject was not large in the auditory region. Furthermore, within subjects, the location of activation foci for a particular stimulus condition was highly consistent. However the location of peak activation for a particular stimulus condition varied substantially across listeners; much more than the anatomy varied. It is established that anatomically specialized brain areas, identifiable on the basis of their microanatomical structure, do not always respect gross anatomical features such as sulci and gyri (Rademacher et al., 2001; see Brett et al, 2002 for a discussion). Our functional results are consistent with this.

To conform to the assumptions of the statistical model used in conventional image analysis, data are spatially smoothed, which confounds extent of activation with intensity of activation. Intense but focal changes in signal are 'smeared out' over adjacent volume elements so that it is difficult to draw conclusions about anatomical specificity. To do so one needs to define anatomical regions of interest, and then explore signal change in unsmoothed data within these regions. This is difficult to do in practice, since brain microanatomy does not respect the gross morphological landmarks observable on structural MR scans (see Brett et al., 2002) for discussion. A promising way to circumvent this problem employs probability maps of cytoarchitectonically defined primary auditory cortex. We have run two preliminary studies exploring this technique (Johnsrude, Cusack, Morosan, Hall, Brett, Zilles, & Frackowiak, 2001; (Johnsrude, Morosan, Hall, Cusack, Brett, Zilles, & Frackowiak, 2001; Johnsrude, Morosan, Cusack, Brett, Ashburner, Zilles, & Frackowiak, 2000), with good results. Further development is planned in section MR2.6 (Methods).

L1.1.4. Separating speech from non-speech

It is commonly assumed that, in the cochlea and the brainstem, the auditory system processes speech sounds without differentiating them from any other sounds. At some stage however, it must treat speech and non-speech sounds differently. In collaboration with Roy Patterson and Stefan Uppenkamp from the CNBH (Cambridge) we used functional MRI to delimit the location of this stage in the auditory pathway by identifying the point where the sound is found to match a specific phonological category. We had previously defined and evaluated a set of synthesised vowel and non-vowel sounds, that were matched for acoustical features but which differ markedly in their similarity to speech (Uppenkamp, Patterson, Johnsrude, Norris, & Marslen-Wilson, 2001). Four of these sounds were used in an fMRI experiment: speech-like with pitch or no pitch, and non-speech-like with pitch or no pitch. Two additional conditions were included as control; these were silence and natural vowels. Sparse imaging with a scan repeat time of 10 sec was used to separate scanner noise and acoustic stimuli in time. When contrasted with silence, all of the sound conditions show very similar activation patterns, centred around Heschl's gyrus bilaterally, with the most prominent peak towards the lateral end of HG. Natural and synthesised vowels, either with or without pitch, did not differ in terms of their activation patterns. There was also no significant activation specific to the (fixed) pitch in either speech or non-speech conditions, indicating that phonological category was a more prominent feature than pitch. There was, however, significantly more activation in the speech-like conditions than in the non-speech conditions, in an area below and posterior to Heschl's gyrus in planum temporale. Whereas this activation is bilateral and symmetric in the group data, single-subject analysis revealed that some listeners show more activation on the right while others show more on the left. This study forms the basis for a more extensive programme laid out in section SL2.

L1.2. Speech segmentation and phonological analysis

The speech signal is continuous, noisy, and variable. It remains a considerable scientific and practical challenge to determine how the listener imposes order on this complex stream of information, and in particular, segments it into appropriate access units at different levels of description. The research summarised here represents three complementary approaches to the use of acoustic-phonetic, phonological, and prosodic cues to lexical segmentation – that is, to the problem of determining the beginnings and ends of words in the speech stream.

L1.2.1. Prosodic cues to lexical segmentation: Bottom-up disambiguation of word-onsets

The lack of acoustic markers of word boundaries in connected speech may create temporary ambiguities between words like cap and the start of longer words like captain. These apparent onset ambiguities have motivated models of spoken word recognition in which lexical competition allows information after the end of an embedded word to assist in identification – typically through competition between non-aligned lexical hypotheses. However, evidence from acoustic-phonetics suggests consistent differences between the syllables in monosyllabic and bisyllabic words. For example, Lehiste (1972) reports significant shortening of the syllable [slip] in words like sleepy and sleepiness. In a series of experiments Davis and colleagues investigated the degree of actual processing ambiguity between embedded words and longer competitors in spoken sentences (Davis, Marslen-Wilson, & Gaskell, 2002). Stimulus sentences for these experiments contained monosyllabic words or frequency-matched bisyllables that contained the monosyllable as the initial syllable (such as the pair cap and captain), placed in a spoken sentence frame ("The soldier saluted the flag with his cap tucked…/with his captain looking…"). An initial gating study showed that duration differences (and possibly other prosodic cues) were able to bias, as appropriate, towards either monosyllabic or bisyllabic interpretations before the end of the syllable. A subsequent series of cross-modal repetition-priming experiments examined in detail the activation of onset-embedded words and longer competitors as the critical syllable and its following context was heard. These showed immediate effects on the relative level of activation of lexical hypotheses according to their compatibility with bottom-up prosodic constraints. This is a significant result which not only underlines the role of fine-grained acoustic detail in the perception and segmentation of connected speech but also demonstrates that onset-embedding may be a less serious computational problem than previous theorists have suggested.

Preliminary simulations illustrate how a recurrent neural network could model the processing of strings containing onset-embeddings when provided with appropriately structured input (Davis, Marslen-Wilson & Gaskell, 2000). Further support for this approach to lexical segmentation and identification comes from simulations that successfully model the relationship between phonological and lexical learning during the development of spoken language comprehension in infants between six and 18 months in age (Davis, in press). The network uses a single learning mechanism and processing resources (hidden units) to learn two different tasks: to predict the upcoming input, and to identify words in the input (requiring lexical segmentation). Rather than competing for processing resources, the combined demands of the two tasks interact to assist learning in the network, leading to more rapid vocabulary acquisition than in networks with the two tasks being assigned separate hidden units. Furthermore, the network shows the expected developmental profile by learning phonological properties of the input before lexical learning, consistent with empirical evidence (Jusczyk, 1999), and by showing gains in the speed of lexical identification during the second year (cf. Fernald, Pinto, Swingley, Weinberg, & McRoberts, 1998).

L1.2.2. The Possible Word Constraint: a new cue to lexical segmentation

This project has concentrated on how listeners make use of cues provided by metrical or phonotactic information, and how these cues interact with the process of lexical competition. It has its origins in earlier work demonstrating that listeners can make use of the onsets of stressed syllables to determine the likely location of word boundaries (Cutler and Norris, 1988). Later work by Norris, McQueen, and Cutler (1995) demonstrated that these effects could be modulated by lexical competition. Research over the last period has extended these findings, and has led to the development of a new model of lexical segmentation.

Norris, McQueen, Cutler, and Butterfield, (1997) presented evidence that listeners make use of what has been labelled the Possible Word Constraint (PWC). Listeners found it easier to detect words in nonsense strings, when extracting the word would leave a residue that could possibly be a real word (e.g. 'see' in 'seeshub', where 'shub' is a phonotactically possible word in English), than when the residue could not be a real word (e.g. 'see' in 'seesh', where 'sh' could not be a word, as it does not contain a vowel). This was modelled by a development of Shortlist (Norris, 1994), in which lexical candidates were penalised if there was no vowel between the end of the candidate and the nearest 'known' boundary in the input, where a 'known' boundary was silence, a phonotactic boundary, or the onset of a strong syllable. This modification also simulated earlier data (McQueen, Norris and Cutler, 1994) on the interaction between lexical competition effects and metrical segmentation (the MSS of Cutler and Norris, 1988) which had previously been simulated by a more complex mechanism. Further work has shown that the PWC is driven by solely by whether or not the 'residue' contains a vowel, and that the identity of the vowel is unimportant. Norris, Cutler, McQueen, Butterfield, and Kearns

(2001) showed that the PWC operated even when the vowel in the residue is a schwa, or a lax vowel. Syllables with schwa or lax vowels cannot be real words in English. This suggests that the PWC is a language-universal strategy, and is guided by consideration of what might be a word in any language, not by whether the residue could be a word in the listener's own language. A strategy like the PWC should be of great value in acquiring language as well as perceiving language as it would provide the infant with valuable information as to the likely location of word boundaries. In accord with this, Johnson, Jusczyk, Cutler and Norris (in press) have found evidence that 12-month-old babies behave in accord with the predictions of the PWC.

L1.2.3. Phonological variation in lexical and sentential context

Regular phonological variation – for example, assimilation of place of articulation – is an important aspect of fluent speech production and recognition, and can be used on-line by the listener as a cue to segmentation (Gaskell & Marslen-Wilson, 1996, 1998). We extended this research to look at the case where phonological variation could generate a natural case of lexical ambiguity involving two normally unambiguous words. For example, in running speech, "a quick run picks you up" can become confusable with "a quick rum picks you up". This is because the coronal place of articulation of the final consonant of "run" assimilates to the labial place of articulation of the initial consonant of "pick", yielding a surface form which is closer to "rum" than to "run". We examined the perception of this kind of change in Gaskell & Marslen-Wilson (2001a; see also Gaskell & Marslen-Wilson, 1999b; Gaskell, 2000a, 2000b). The results supported previous research in demonstrating the importance of evaluating phonological alternations in their phonological context, but also demonstrated a strong effect of sentential context on resolution of this kind of ambiguity. This provides a bridging link between models of spoken word recognition and lexical ambiguity resolution.

A second strand of research in this area examined the effects of resyllabification and phonological liaison in the perception of French. The dominant model of speech perception for French emphasises the role of the syllable as a segmentation and access unit. When vowel initial words are embedded in fluent speech the syllable model predicts that natural resyllabification processes such as liaison should impede recognition of these words. Our research demonstrated the opposite effect (Gaskell, Spinelli & Meunier, in press; Spinelli, Gaskell & Meunier, 2000), and showed that, as in English, sensitivity to the phonological context of regular variations in speech is a crucial component of the recognition system. The results suggest that the role of the syllable in models of speech processing for Romance languages should be refined.

L1.3 Architecture of spoken word recognition

A topic that continues to be of central importance to research in spoken word recognition is the overall architecture and structure of the recognition system. For example, can speech recognition be considered to be a series of autonomous and modular processes, or should it be characterised as a highly interactive system? Naturally, this question cannot be answered without also considering the nature of the processes and representations involved in spoken word recognition. The research reported under L1.3.1 and L1.3.2 addressed both the broader architectural issues and more specific questions about the nature of the representations of phonological form. Project L1.3.3 reports promising new research using fMRI techniques to probe the organisation of neural systems involved in speech comprehension.

L1.3.1. Shortlist and Merge: Issues in lexical architecture

A particular issue in the architecture of the speech recognition system is whether pre-lexical (phonemic or phonetic) processing can be influenced by top-down feedback from the lexicon. The dominant view in the literature has been that there must be feedback from the lexicon to prelexical processes. This is a superficially plausible position because there is extensive evidence that listeners' ability to make phonological decisions is influenced by lexical information. Furthermore, many researchers believe that lexical feedback is to be expected because it will help recognition. However, the fact that phonological decisions can be influenced by lexical information does not necessarily imply that there is feedback. The view that feedback will help recognition of speech sounds has been based largely on intuition rather than on any formal analysis of the problem.

The most significant product of this work, which continues a long-standing collaboration with Cutler and McQueen (Max-Planck Institute, Nijmegen) has been an influential Behavioral and Brain Sciences paper (Norris, McQueen, and Cutler, 2000a, 2000b), which argued that speech recognition is a feed-forward process in which pre-lexical processing is not subject to any feedback from lexical processes. The paper also presented a new computational model (Merge) of the process by which listeners perform phoneme identification judgements in speech recognition tasks. In an extensive review of the literature on feedback in speech recognition we pointed out that the idea that lexical feedback should be helpful in speech recognition was misguided. Contrary to the popular view, feedback can not be of any help in on-line word recognition. Additionally, we described how the data cited as evidence for feedback could be explained by a bottom-up model. In order to explain some of the data that appeared to demonstrate feedback we developed a new computational model of phonetic decision making (Norris, McQueen, and Cutler, 1999, 2000a, 200b; Norris, 2001). This new model – Merge, is a development of Shortlist (Norris, 1994). The central feature of Merge is that it explains lexical influences on phonetic decision making in terms of a decision mechanism that combines information from both lexical and pre-lexical levels. We show that there is behavioural, neuropsychological and neuroimaging evidence that the processes responsible for making phonological decisions are not the same as those responsible for prelexical processing in comprehension. We also presented arguments to show that all models must have something analogous to the decision component of Merge. Therefore, by dispensing with lexical feedback, Merge provides a more parsimonious account of the data than alternative interactive models. One further achievement of this paper is that it establishes a set of criteria that specify what would constitute evidence against a modular feed-forward account of spoken word recognition. This will enable researchers to focus on the critical issues distinguishing feed-forward models and feedback models.

Critical data on lexical effects in phoneme categorisation that provided much of the motivation for the development of Merge was reported in McQueen, Norris and Cutler (1999a). That paper examined lexical effects in subcategorical mismatch, that had been studied earlier by Marslen-Wilson and Warren (1994). Our study produced two critical results. First, we confirmed that lexical competitors could have an inhibitory effect on phoneme identification in non-words. This result, combined with other data in the literature, forced us to reject the Race model of phoneme identification proposed by Cutler and Norris (1979). According to the Race model, phoneme identification is performed by a race between lexical and prelexical routes. Phoneme identification in non-words can only be performed by the pre-lexical route, and should therefore not be influenced lexical effects of any sort. A second important finding was that small changes in the experimental procedure could make the inhibitory lexical effects appear or disappear. They could not therefore be an automatic consequence of the speech recognition process as suggested by Marslen-Wilson and Warren. Finally, we presented arguments to show that, contrary to Marslen-Wilson and Warren's claim, the data were consistent with explanations based on lexical competition.

A number of other papers (Cutler, Norris and McQueen, 2000; McQueen, Cutler and Norris, 1999, 2000a, 2000b, in press; McQueen, Norris and Cutler, 1999b, 2001; Norris, 1999,2001; Norris, Cutler and McQueen, 2000) have also reported data, theoretical arguments, and simulations to support the general conclusion that speech recognition is a bottom-up process.

Feedback in perceptual learning

A central part of the Merge argument against lexical involvement in pre-lexical processing is that it cannot help on-line recognition. This does not, however, exclude the possibility that lexical information can be of benefit in learning or modifying phonemic categories. This possibility rests on the theoretical distinction between the immediate on-line activation feedback, as incorporated in TRACE and other interactive-activation models, and the feedback responsible, over the longer term, for learning (see Norris, 1993, for discussion). For example, a standard 'feed-forward' back-propagation network classifies its input in a completely feed-forward manner, but learns by feeding an error signal back down the network. There can be feedback for learning in the absence of feedback for on-line processing.

We have studied this by presenting listeners with stimuli containing ambiguous phonemes - half way between /f/ and /s/ - which can appear either in non-words, or in contexts where lexical information can bias the interpretation of the ambiguous phoneme (e.g. cara?, where interpreting /?/ as /f/ would make the word 'caraf' whereas interpreting it as /s/ would make a non-word). When these ambiguous phonemes appear in words, listeners subsequently identify these phonemes as instances of the lexically determined phoneme (McQueen, Norris, and Cutler, 2001; Norris, McQueen, and Cutler, submitted). The use of lexical information for learning has considerable value in helping listeners adjust to the different phonemic categories used by speakers with different accents or unusual speaking styles. The experimental effects are very large, and emerge over the course of hearing only 20 instances of the ambiguous phoneme. This work suggests that listeners use top-down lexical information when it is useful (in learning) but not when it is not (during on-line perception).

Lexical activation in continuous speech.

Models of continuous speech recognition such as Shortlist and TRACE assume that, during the course of speech recognition, many candidate words are accessed (possibly including several tokens of the same word), and that these candidate words compete with each other to determine the final analysis of the input. There is now extensive empirical support for this claim (e.g. McQueen, Norris and Cutler, 1994). One consequence of this competition process is that when a word like 'trombone' is heard, activation of 'trombone' should inhibit activation of the lexical candidate representing 'bone'. However, some studies in the literature (Shillcock, 1990) have reported that when the word 'trombone' appears in a sentence, 'bone' is activated, as indexed by cross-modal semantic priming. If this result is reliable, it could imply that the theories are wrong. On the other hand, it could imply that semantic priming follows simply from accessing the word 'bone' in the lexicon, even if that word candidate is subsequently inhibited. To examine this we performed a series of cross-modal priming experiments (Norris, Cutler and McQueen, in preparation), using both semantic and identity priming, and using both sentences and isolated words. In semantic priming the comparison was between priming from bone->rib, or trombone->rib. There was no evidence for semantic activation of the embedded word 'bone' in 'trombone' in any of 5 semantic priming experiments, although 'bone' did produce priming when presented as an isolated word. In fact, in sentences we found semantic priming from the word 'bone' itself in only one experiment where we employed a manipulation of contrastive stress. We did find evidence of identity priming in sentences. Most significantly, the priming was facilitatory for 'bone' itself, but inhibitory for 'bone' in 'trombone'. That is, it appears that bone is accessed and then suppressed, exactly as would be expected by lexical competition. That is, identity priming appears to be driven by the activation of lexical candidates, not lexical entries themselves. The absence of semantic priming in sentences is consistent with earlier work at the MRC-APU by Williams (1988), and, indeed, with the failure of 'trombone' to prime 'bone' in previous replications reported by Marslen-Wilson, Tyler, Waksler, & Older (1994)

Phonological priming

In recent years, a number of studies have examined phonological priming effects as a means of investigating the form of the phonological representations underlying spoken word recognition. One puzzling feature of the data has been that lexical decision and naming paradigms produce somewhat different patterns of results. For example, priming by rhyme overlap (cat-mat) is much larger in lexical decision than in naming. In lexical decision only words benefit from priming, whereas in naming both words and non-words benefit. We examined the possibility that much of the phonological priming effect in lexical decision might be strategic (Norris, McQueen and Cutler, 2002). To study this we manipulated the nature of the filler trials in a phonological priming experiment. When we included targets which almost rhymed with their primes (foils, e.g., bulk-SULSH) facilitation for rhyming targets was severely attenuated in lexical decision, but not in naming. Subjects appear to have a bias to respond 'yes' to rhyming trials in lexical decision, and this bias can be attenuated by including foils that discourage this strategy. Nevertheless, there appears to be a residual automatic effect of phonological priming in lexical decision that is similar in size to that observed in naming.

L1.3.2 The Distributed Cohort Model

One of the leading models of spoken word recognition is the Cohort model, which has evolved considerably over the past two decades (Marslen-Wilson & Welsh, 1978; Marslen-Wilson, 1987). More recently, on the basis of arguments made by Marslen-Wilson and Warren (1994), the model has assumed a distributed computational substrate, and has proposed a distinctive processing architecture, where both phonological and semantic representations are seen as the output of the system. Gaskell, working in collaboration with Marslen-Wilson, has taken the lead in implementing a connectionist model of spoken word recognition with these general characteristics. This model (the Distributed Cohort Model or DCM) has a number of significant features. First, it dispenses with the commitment to pre-lexical integration of speech information into segmental or syllabic units found in almost all models of speech perception. Second, it defines lexical activation in terms of an output representation of both lexical content (meaning) and lexical form (phonology), rather than in terms of abstract recognition units. The predictions of this model for the parallel activation of spoken words were analysed in

Gaskell & Marslen-Wilson (1999a; 2001b), and are examined experimentally below. The predictions of the DCM with respect to integration of subphonemic cues during lexical access are examined in Gaskell (2000c). The DCM has achieved recognition as one of the principal models of spoken word recognition over the course of the review period, and is gaining empirical support (Gaskell & Marslen-Wilson, 2002; Rodd, Gaskell, & Marslen-Wilson, 2002).

Dynamics of lexical competition during speech comprehension

The distinctive feature of the DCM is the claims that it makes about the detailed structure of lexical competition between co-activated word-candidates during spoken word recognition. In contrast to models that represent competing lexical activations using localist word nodes, the DCM instantiates a model of lexical access where a featural representation of speech is mapped directly on to a distributed lexical representation. This type of representation can only capture multiple lexical candidates as overlapping patterns of activation, in a so-called "blend" pattern (Gaskell & Marslen-Wilson, 1999a, 2001b) This blend will only represent multiple candidates successfully to the extent that they have similar representations. For spoken words, this is true if lexical representations are organised in terms of their phonology – members of the same word-initial cohort. However, if the same words are represented in terms of their semantics, which will vary widely, the blend pattern will be much less successful in representing the properties of individual words. According to the DCM, lexical representations are organised both in terms of phonology and meaning. This means that the effects of competition on parallel activation will vary across these dimensions of the distributed representational space, with competition having much stronger effects, for the same words, on the coherence of semantic representations as opposed to phonological representations.

We tested these predictions in a series of cross-modal priming tasks, where word fragments that varied in ambiguity (i.e. number of competitors) were evaluated in three different priming situations (Gaskell & Marslen-Wilson, 2002). A fragment like "garm" from garment is already relatively unambiguous and compatible with few other possible words. A matched fragment like "capt" from captain is much more ambiguous, and remains ambiguous for longer. These variations in competitor environment had little effect on the strength of priming when the relationship between prime and target was primarily lexical and phonological, as in a straightforward repetition priming task (garm/garment). However, when the relationship was semantic rather than phonological, as in garm/clothes, so that the task probed the ability of the system to capture the specific semantic properties of the prime, then the effects of competition were much stronger. Primes like "garm" or "husb" that had fewer competitors, primed reliably more strongly, and earlier in the word. The ambiguous primes were unable to elicit priming until much later – after the end of the word in fact, when all competitors were ruled out. These contrasting effects follow directly from the DCM representational assumptions, and are not obviously predicted by any of the current competing models.

Semantic competition in lexical access: making sense of ambiguity

A key property of the DCM, in common with a number of other models (e.g., Plaut & Shallice, 1993) is that word recognition involves activation of meaning representations, so that competition between semantic representations plays as important a role in lexical access as does competition between orthographic or phonological form representations (or, indeed, abstract lexical nodes). This means, in turn, as we indicated in the previous section, that activation of dissimilar semantic representations will slow down the recognition process. This should strongly affect ambiguous words like bark, which have two quite unrelated meanings. They should be identified more slowly than unambiguous words like soap. The existing literature, however, contains several reports indicating an ambiguity advantage, with faster response times to ambiguous words in lexical decision tasks (e.g., Azuma & Van Orden 1997; Pexman & Lupker, 1999). This seems to present severe difficulties for theories in which semantic competition is a necessary consequence of their processing architecture.

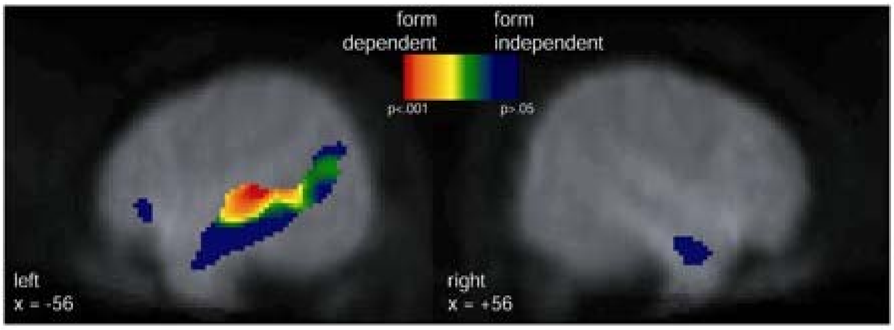
In recent research, however, we have been able to show that a true ambiguity advantage does not exist, and that previous results were based on a failure to separate out ambiguity due to multiple senses from ambiguity due to multiple meanings (Rodd, 2001; Rodd, Gaskell, & Marslen-Wilson, 2002). Words with multiple senses, unlike words with multiple meanings (such as bark), share a range of separable but similar meanings. The word twist for example has several senses (as in 'twisting your ankle' as opposed to 'twisting the truth'), but they all share a common semantic core. In a series of experiments, using lexical decision to both visually and auditorily presented words, where sense and ambiguity were factorially co-varied, we showed that multiple senses did indeed speed responses, but that multiple meanings had the opposite effect, slowing down responses. Analyses of the stimulus sets used by earlier researchers (e.g., Azuma and Van Orden, 1997) showed that they had confounded sense and meaning, so that sets showing an ambiguity advantage were those where ambiguity was counted in terms of number of senses rather than number of separate meanings. The importance of this result is not so much that it rules out alternative models (for discussion see Rodd et al, 2002), as that it removes an apparent empirical obstacle to the viability of recognition models based on distributed semantic representation. In new research, furthermore, Rodd has demonstrated that network models are capable of capturing both the detrimental effect of multiple meanings and the facilitatory effect of multiple senses – in the latter case because the network forms broader attractor basins, allowing inputs to settle more quickly into the correct attractor (Rodd, Gaskell, & Marslen-Wilson, 2001; submitted).

L1.3.3. Processing distorted speech: Neuro-imaging evidence for hierarchical processing.

A striking property of speech comprehension is its resilience in the face of the background noise, signal degradation, and variability that pervades everyday speech. The robustness of comprehension reflects both the ability of the system to adapt to variation and the redundant coding of information in spoken language. Most phonetic distinctions are carried by multiple acoustic cues and comprehension can be maintained when any single source of information is lost. In a recent fMRI study, we have capitalised on this informational redundancy and used several forms of distortion to observe the neural response common to partially intelligible speech (Davis & Johnsrude, submitted; Johnsrude, Davis, Dilks, & Turnbull, 2001). By comparing responses to acoustically different but still intelligible speech we could separate those neural systems that process the sounds of speech (which may respond differently to acoustically different forms of distortion) from areas that respond to more abstract, higher-level information that is present in all forms of intelligible speech. Furthermore, we could explore the neural correlates of processes that compensate for distortion, recovering meaning from distorted input.

In this study, three forms of artificial distortion were used, each of which provides a different challenge to the processes of spoken language comprehension: (1) speech was presented in continuous background noise, (2) speech was interrupted by noise or (3) the spectral detail of speech was replaced by noise. Behavioural testing allowed us to develop three levels of intelligibility for each form of distortion, such that sentences could be presented from which participants could repeat around 90%, 60% or 20% of the words correctly. We used fMRI to measure the neural response to sentences presented with these different forms and levels of distortion, as well as clear speech and unintelligible, amplitude-modulated noise. Activation correlated with the intelligibility of the presented sentences in anterior temporal regions bilaterally, in more posterior temporal regions on the left, in the left hippocampus and in the left inferior frontal gyrus (see Fig L2).

Figure L2: Lateral view of brain areas showing a significant response to increasing intelligibility of auditorily presented sentences in Davis & Johnsrude (submitted). Activation is shown superimposed on the mean EPI image across subjects at $p < 0.001$ uncorrected. Colour scale shows intelligibility-responsive regions which showed a reliable difference between the three forms of distortion (form-dependent activation at $p<.001$ is shown in red) or no reliable difference between distortions (form-independent activation at $p>0.05$ in blue).



Differences in the neural response to the three forms of distortion (independent of intelligibility) indicate sensitivity to the acoustic form of the signal. We observed a response in middle portions of the superior temporal lobe, lateral and inferior to primary auditory cortex, which although correlated with intelligibility, also differed between the three types of distortion. This finding provides compelling evidence for hierarchically organised processing of spoken stimuli in lateral regions of the temporal lobe. Within (probable) secondary auditory cortical regions we observe a response to the sound properties of spoken sentences, while anterior and posterior regions of the temporal lobe were insensitive to sound properties, responding only to the intelligibility of spoken sentences, and not their acoustic form.

Comparing brain activation to distorted speech with responses to clear speech and to unintelligible noise revealed a number of areas in which activation was increased when comprehension was more difficult or effortful. These regions were entirely left lateralised, including the temporal lobe, thalamus, and an extensive region of the frontal lobe, including the inferior frontal gyrus and regions of premotor cortex. These activated areas partially overlapped with temporal lobe and frontal lobe regions in which response correlated with intelligibility as well as areas which showed a differential response to the three forms of distortion. These findings are consistent with the recruitment of additional low-level, sound-based processes as well as higher-level, linguistic and/or attentional processes in the comprehension of distorted speech.

Adaptation to noise-vocoded speech in normal listeners

In a related subsequent study, we have used behavioural techniques to lay the foundations for further research into the mechanisms underlying adaptation to speech distortions. An additional interest here was that noise-vocoded speech (Shannon, Zeng, Kamath, Wygonski, & Ekelid, 1995) simulates the temporal information preserved by cochlear implants (CI), and has been used to model the perception of CI-processed speech in normal listeners (Rosen, Faulkner, & Wilkinson, 1999). In this work, we explored how listeners learn to understand noise-vocoded speech: factors such as acoustic or lexical feedback that influence this form of learning may suggest ways to assist the rehabilitation of CI users.

We conducted two experiments in normal listeners, measuring the intelligibility of 6-channel, noise-vocoded sentences, to assess the effect of different training schemes. Comprehension was assessed by measuring the proportion of words from each sentence that listeners were able to report correctly. Across experiments we varied the ordering and the type of feedback that listeners heard during the training period. The most striking results were for training blocks that used "jabberwocky" sentences. These were phonotactically legal nonword sentences matched on length and prosodic contour to a comparison set of normal sentences ("the police returned to the museum" became "cho tekine garund pid ga sumeun"). Listeners pre-exposed to jabberwocky sentences performed no better than naïve (untrained) listeners, suggesting that higher-level word- or meaning-based information is required for this kind of perceptual learning to occur. A proposal for continuing this work is given in section SL5.2. of the future proposals.

L1.3.4 Cortical interactions in processing lexical ambiguity in sentential context

To understand the meaning of a sentence, we need to put together the meanings of its constituent words. This made more difficult by the presence of ambiguous words. For example, in a phrase such as "the loud bark", the listener needs to work out that the noun "bark" refers to the "bark of a dog" and not the "bark of a tree". Processes that select appropriate interpretations on the basis of the context are extremely important; over 80% of the common words listed in dictionaries are given more than one definition (Rodd et al, 2002). In a pioneering study, collaborative with Rodd (CSL, Cambridge), we have begun to investigate the neural substrates of these combination processes (Rodd, Davis, & Johnsrude, 2002).

We used fMRI and sparse imaging to scan volunteers while listening to sentences that contained ambiguous words (e.g. "the shell was fired towards the tank") and matched, unambiguous sentences (e.g. "her secrets were written in her diary"). Comparing brain areas activated by these two types of sentences revealed increased processing for ambiguous sentences in three brain regions: the posterior left middle temporal gyrus, and the left and right inferior frontal gyri. This points to a combined role of frontal and temporal lobe systems in activating, selecting and combining the meaning of words in natural speech comprehension. Current views of the domains of functioning of these areas suggest that the temporal region supports the access and storage of semantic information about individual words, whereas frontal regions support control functions involved in the selection and combination of these meanings.

Project L2: The structure of lexical representation

Scientific direction: Marslen-Wilson (80%), Pulvermuller (5%)

MRC Research support: Boudelaa (100%), Davis (20%), van Casteren (50%), Shtyrov (5%), Hauk (5%), Reid (100%)

Externally funded: Meunier (100%), Zhou (100%)

Students: Reid (100%), Chou (100%), Rodd (100%), Ford (100%)

At the core of the language system is the mental lexicon, the mental representation of the forms and meanings of the words and morphemes in a language. These representations play a central role in processes of language comprehension and production, mediating between the processes of speech analysis and the computation of meaning. Our focus in the first main project here (L2.1) is on the structure of these representations: whether the mental lexicon is organised in terms of whole-word representations, or whether the representation is predominantly morphemic in character. We approach these issues cross-linguistically, in order to investigate a representative range of possible lexical and morphological systems, and report systematic comparisons across a wide range of different language systems, including Arabic, Polish, and Chinese (as well as English).

The second main focus here, in project L2.2, is on the contrast between regular and irregular inflectional morphology in English. This has come to be viewed as a crucial test case for fundamental disputes about the appropriateness of symbolic as opposed to subsymbolic modes of mental computation. Earlier work by Marslen-Wilson and Tyler (1997) demonstrated a neuropsychological double dissociation between the processing of regular and irregular past tense morphology in aphasic patients. The further work reported here, carried out chiefly in collaboration with Tyler and colleagues (Centre for Speech and Language, Experimental Psychology, Cambridge), has strengthened and broadened the basis for these dissociations, working with a variety of brain-damaged populations and using neuro-imaging techniques to study these phenomena in the intact adult brain. In addition, cross-linguistic studies of regularity and irregularity in French and Polish help to put the phenomena for English in an appropriate perspective.

L2.1 Cross-linguistic studies of lexical structure: Word formation and derivational morphology

An adequate account of spoken language comprehension is going to require a convincing definition of the notion "word". To provide such a definition we need a better understanding of the structure of the mental lexicon – what are its basic units of representation and analysis, and how are these organised in relationship to each other? Any attempt to resolve these questions is immediately confronted with the immense variety of lexical arrangements across languages. The research summarised here represents a systematic and on-going attempt to explore and describe this cross-linguistic variation. Do we find evidence for common underlying principles in lexical organisation. The results so far suggest that lexical systems are as notable for their differences as for their similarities.

The starting point is a view of lexical organisation developed initially in the context of English derivational morphology (Marslen-Wilson et al, 1994). Derivational morphology, in a language like English, is the concatenation of a base form (a root or a stem) with one or more derivational affixes. These may be suffixes or prefixes, as in forms like happiness, analysable as {happy} + {-ness}, or rethink, analysable as {re-} +

{think}. These derivational processes change the meaning, and often the form-class of the stem, and are generally thought of as generating new lexical items.

Using a variety of immediate and delayed repetition priming techniques, we have developed a view of the English mental lexicon as a dynamic cognitive entity, distinguished by three core properties: (a) We assume that it is morphemically organised, so that the basic unit of representation is the morpheme, and complex words, where synchronically decomposable, are represented in terms of their constituent morphemes; (b) It is combinatorial, indicating that the same morpheme combines with other morphemes across a morphological family, to create the basis both for meaning and for structure. Thus, the morpheme {dark} in darkness is the same lexical and cognitive entity as the {dark} in darkly. Similarly, the {–ness} in darkness is the same as the {–ness} in toughness. (c) Morphemic decomposition is assumed to be dependent on semantic transparency. Complex forms are only represented in morphemic format if they are semantically transparent. The form punishment is semantically transparent and represented as {punish} + {-ment}. The form department, although superficially also complex, is semantically opaque and is represented as a whole form.

The evidence for these claims about English comes from a set of priming effects, the most salient of which are the following:

Stem priming: This is the priming effect, found in masked priming and in immediate and delayed repetition priming (Marslen-Wilson et al., 1994; Marslen-Wilson & Zhou, 1999), between a semantically transparent complex form and its stem, as in prime/target pairs like darkness/dark. Critically, semantically opaque pairs like department/depart do not prime.

Affix priming: This is the priming effect between semantically unrelated prime-target pairs which share the same affix, as in darkness/toughness and rebuild/rethink (Marslen-Wilson, Ford, Older, & Zhou, 1996). This is strongest for productive affixes, and is interpreted as the combinatorial re-use of the same bound morpheme in both prime and target.

Suffix-suffix interference: This is the interference effect observed between semantically transparent pairs sharing the same stem but different suffixes, as in darkness/darkly (Marslen-Wilson et al., 1994; Marslen-Wilson & Zhou, 1999). The absence of priming between these highly semantically and morphologically related pairs is interpreted as inhibition between two affixes competing for linkage to the same stem.

The co-occurrence of these three effects we take to be diagnostic of a decompositional and combinatorial system. How far do we find similar effects in other languages?

L2.1.1. Polish

The first language we report on is Polish, a Slavic language with an exceptionally rich morphological system, and which also, like English, employs a concatenative derivational morphology, combining stems with sequences of prefixes and affixes. Unlike English, essentially all surface forms are morphologically complex, combining a bound stem with one or more suffixes. Thus the word przybiegłam 'I run up' consists of the stem 'bieg-', the derivational-aspectual prefix 'przy-', and the inflectional suffixes '-ł' and '-am', indicating the past tense and the 1st person singular feminine. In a series of studies, chiefly using delayed repetition priming tasks to reduce semantic effects, we have found a profile of results that is very similar overall to English (Reid, 2001; Reid & Marslen-Wilson, 2000; in press).

Stem priming: We find strong stem priming in both simple and complex forms, ranging from pairs like chodz-enie/chodz-i-ć (walking/to walk) to highly complex forms like bajk-o-pis-ar-stwo/pis-a-ć (fable-writing/to write).

Affix priming: We also find priming for pairs sharing the same affix. This covers sets of pairs sharing derivational affixes, as in kuch-arz/piłk-arz (a cook/footballer) sharing the agentive suffix {-arz}, as well as more complex forms like roz-pakow-ywa-ł-em (to unwrap, 1st person sing., masculine, past tense) and roz-wałkow-ywa-ć ('to flatten something using a rolling-pin). These words share a derivational aspectual prefix {roz-} and the secondary imperfective suffix {ywa-}, and show strong priming even with 12 items intervening between prime and target.

Suffix-suffix interference: Polish shows strong interference effects of this type. Pairs like pis-anie/pis-arz (writing/writer) and balon-owy/balon-ik (balloon-like/a little balloon) show no priming at all in delayed repetition, despite their close morphological and semantic relationship.

Semantic transparency: Finally, Polish shows strong effects of semantic transparency. As in English, there is no priming for semantically opaque pairs that historically shared the same stem, as in pairs like jałowiec/jałowy (juniper/futile), with some indication in further tests that strict semantic compositionality may play a stronger role in determining representation than in English.

The profile of results for the different kinds of priming relationships suggest that Polish and English have a great deal of common. Although they are very different languages in many important respects, they both fit an overall template that we interpret in terms of a morphemically organised and combinatorial mental lexicon.

L2.1.2 Arabic

Semitic languages like Arabic and Hebrew possess a complex morphological system that is organised on fundamentally different principles to languages like English, French, and Polish, with their concatenative morphological processes. Semitic languages, in contrast, employ a non-concatenative morphology, where the surface phonetic form is constructed by interweaving two or more abstract morphemes - the consonantal root, carrying semantic information, and a word pattern which specifies the syntactic category and the phonological structure of the surface form. Thus, for example, the Arabic root {ktb} with the semantic value of <writing>, combines with the word pattern {faℵala}, with the syntactic meaning of 'active verb', to give the surface form kataba, meaning 'write'. These are highly abstract morphemes, that never surface as phonetic forms on their own. The question we investigated was whether these abstract entities function cognitively in ways comparable to stems and derivational morphemes in concatenative morphologies such as English.

Root priming: Using cross-modal and masked priming techniques, we found clear evidence for priming between pairs that shared the same consonantal root (Boudelaa & Marslen-Wilson, 2000a). Thus, for example, the prime /ʔidxaalun/ (inserting) speeds responses to the target /duxuulun/ (entering), where prime and target have in common the root {dxl}. Strikingly, and quite differently from English and Polish, priming is just as strong when the prime is semantically opaque, as in the form /mudaaxalatun/ (interference), which also shares the root {dxl} with the target /duxuulun/, but where the meaning of the form is not synchronically predictable. This preservation of root priming under conditions of semantic opacity shows up consistently across all our experiments, and is also found for Hebrew (e.g., Frost, Forster, & Deutsch, 1997).

In contrast with English, however, a further level of more abstract semantic analysis plays a role in lexical organisation. In addition to the tri-consonantal root, such as {ktb} and {dxl} mentioned above, we also find evidence for more abstract bi-consonantal morphological unit called the etymon. For example, in the form [batara] the core meaning is carried not by the tri-consonantal root morpheme {btr} but by the etymon morpheme {b,t} which surfaces in other forms like [batta] (sever), [batala] (cut off) with the same meaning <cutting>. In a series of priming experiments we show that the etymon can yield the morphological priming effects typically obtained with triconsonantal root morphemes. Two words sharing an etymon facilitate each other even though they do not share a root (Boudelaa & Marslen-Wilson, 2001a)

Word pattern priming: Analogously to affix priming, we find significant effects between pairs that share the same word-pattern but have different roots and different meanings (Boudelaa & Marslen-Wilson, 2000b), as in pairs like /xudℵuuℵun/ and /□uduuTun/ (submission/happening), sharing the word pattern {fuℵℵuulun} (with the meaning "deverbal noun, singular"). The absence of priming between forms like /suZuunun/ and /□uduuTun/ (prisons/happening), which have word patterns that are phonologically but not morphologically identical, demonstrates the morphological nature of the effects here, and rules out an account in terms of phonological overlap between prime and target.

These results for Arabic, and the comparable results for Hebrew, suggest strong support for a decompositional, combinatorial system, with abstract morphemes combining to produce the surface form, and being separated out in the process of recognition. The complete absence, however, of a semantic transparency effect in root priming, signals an apparent fundamental difference in the principles underlying the role of morphological combination.

In addition, further experimental analysis of the word pattern revealed that these priming effects were mainly being driven by the CV-Skeleton, a highly abstract structural unit coding the phonological shape of the surface word and its primary syntactic function (McCarthy, 1981, 1982). In three experiments using masked, cross-modal, and auditory-auditory priming we examined the role of the CV-Skeleton as a morphemic unit in the processing and representation of Arabic words. Strikingly, word pairs sharing only the CV-Skeleton primed reliably throughout, with the amount of priming being as large as that observed between pairs sharing the full word pattern (Boudelaa & Marslen-Wilson, submitted). This is important not only because of the abstractness of the psycholinguistic entities thus identified, but also because this is a type of morpheme for which there is no counterpart in languages like English. Although the CV-Skeleton does play a role in English, it does so only as a phonological entity, and does not carry meaning.

Time-course of morphological activation in Arabic and English

In priming studies of morphology, it is an important issue to separate out potential confounds due either to form overlap between prime and target or to semantic overlap. One way of assessing these issues is to use incremental masked priming, where the exposure duration of a masked prime is systematically varied to determine the time-course with which orthographic, morphological, and semantic factors come into play. In earlier work in English, carried out collaboratively with the CSL (Cambridge), we found that morphological structure plays a dominant role in structuring lexical representations at all stages of processing (Rastle, Davis, Marslen-Wilson & Tyler, 2000). Varying SOA over the range 43, 72, and 230 ms, we found morphological effects (for pairs like sadness/sad) at all SOA's. These were just as strong as identity priming effects. Semantic effects did not appear reliably until the longest SOA, while there was some evidence for transient form-based effects at the shortest SOA.

This paradigm can readily be transported into Arabic, where it is important not only to evaluate the time-course with which different factors come into play, but also to probe the morphological analysis processes involved in the analysis of Arabic forms into word-patterns and roots. Accordingly, we varied the morphological (word pattern, and root), orthographic, and semantic relationship between prime and targets over four closely spaced SOA conditions (32, 48, 64, and 80 ms). The results show distinctive patterns of activation for the two morphemes (Boudelaa & Marslen-Wilson, 2001b). Word pattern effects are transient and detectable only at intermediate SOA's (48-64ms). Robust root effects are evident at all four SOA's, and are unaffected by factors of semantic transparency. However, the pure effects of semantics, for the semantically related items, are only seen at the longest SOA, comparable to the English results. Unlike English, however, we do not see good evidence for form-based effects at the earliest SOA. More generally, the patterning of different effects over time, and the separability of word-pattern and root effects, argues strongly that morphological effects in Semitic languages represent distinct structural characteristics of the language, and are not reducible to form or meaning overlap.

L2.1.3 Compounding in Chinese and English

A final set of comparisons involve compounding, a quite different procedure for word-formation, and where the starting point is Mandarin Chinese, rather than English. Compounding is a highly productive means of word formation in both English and Mandarin. Unlike derivational word formation, it does not involve the combination of a stem with an affix, but the linkage of two free stems – as in the English compound houseboat, made up of the two nouns house and boat. The effect of this, in contrast to derivation, is that compounding is not fully compositional or combinatorial in nature. The meaning of a compound is never fully predictable from the meaning of its components - although a snowman is a man made of snow, a milkman is not a man made of milk, and so forth. To know what a compound means, one needs to know what it refers to. The issue, that we addressed first in Mandarin and then in English, is whether this leads to a whole-word, rather than a decompositional and morpheme-based representation of compounds in the mental lexicon.

Compounding in Mandarin takes place in a functionally very different linguistic environment from English. Mandarin has essentially no derivational morphology, so that compounding is its only productive means of word-formation, under conditions where there is considerable pressure due to homophony at the syllabic level. Recent analyses suggest that around 70% of word types in Mandarin are bisyllabic compounds (Institute of Language Teaching and Research, 1986). In a series of collaborative studies with Zhou (Cambridge, Beijing) we addressed the issue of whether a morphemic account or a whole form account was appropriate (Zhou & Marslen-Wilson, 1995; Zhou, Marslen-Wilson, Taft, & Shu, 1999; Zhou & Marslen-Wilson, 2000). Mandarin seemed to be a plausible candidate for a morphemic account, because of the salience of individual morphemes in the spoken language and in the writing system. Extensive research using auditory-auditory repetition priming shows that such an account is not correct. Compounds are represented as separate lexical entries, and not as combinations of their constituent morphemes. This means that Mandarin, unlike the other languages we have studied, does not have a system of word-formation that is decompositional and combinatorial.

This raises the question of how English compounds are represented, which we investigated in a series of cross-modal experiments, looking at the priming relations between transparent (bathroom), opaque (blackmail), and pseudo (shamrock) compounds and their constituent morphemes (Zhou & Marslen-Wilson, 2000). Two results in particular seem hard to handle for a morphemic story. The first is that we did not find priming between the first and second constituents of a compound. Thus bath, for example, does not prime tub. This is quite inconsistent with the view that compounds are represented as strengthened links between their constituent morphemes. The second finding is that shared constituents between transparent morphemes do not lead to priming unless the compounds as a whole are semantically related. Thus headache does not prime headscarf, even though they both transparently contain the morpheme head. In contrast, teacup does prime teapot. This is because these two compounds are strongly semantically related, whereas headache and headscarf are not. This is not consistent with a morphemic, combinatorial story, where the morpheme head is a constituent of headache and headscarf in the same way that punish is a constituent of both punishment and punishable. In summary, compounding in Mandarin and English seem to be remarkably similar, reflecting in the same way the representational consequences of the unpredictability of the meaning of compounds.

Summary

Despite the small sample of languages studied, we are left with a wide range of lexical arrangements. Mandarin Chinese seems to lie at one extreme, with apparently no combinatorial procedures for word-formation, and with a lexicon made up of whole forms, in which compounds and the words that make up these compounds all have separate lexical representations. English has a similar system for compounding, but also has a decompositional system of word-formation and representation, reflecting the different processing requirements of derivational procedures that operate on a combinatorial basis, and that deliver predictable and compositional meanings. In this respect English parallels the broad characteristics of a language like Polish, which has a much richer and more complex morphological system. Both of these languages, nonetheless, share with Arabic (and Hebrew) a combinatorial and decompositional approach to lexical representation. In these Semitic languages, however, morphological representation appears to play a more fundamental structural role, so that no surface form can be produced without some underlying process of morpho-phonological combination. This delivers both the surface form, and its basic syntactic and semantic properties.

These differences in lexical representation, although reflecting only a preliminary sample of languages, and reflecting a single type of experimental approach, nonetheless suggest that unitary models of spoken word access processes may not be possible across languages. Although all lexical systems must share the same underlying cognitive and neural constraints on representation, process, and acquisition, these constraints seem to be sufficiently broad to allow different systems to be constructed on apparently quite different organisational principles.

L2.2 Regular and irregular inflectional morphology: Issues in the architecture of the human language system

A key issue in cognitive neuroscience is the functional and the neural architecture of the systems underlying human language, and whether the organisation of these systems should be characterised in terms of a uniform overall computational and neural process, or whether multiple and distinct underlying mechanisms are involved. A particular empirical focus for this issue has been the irregular and regular forms of the English past tense, which provide a sharp contrast in the demands that they make on processes of language learning, comprehension and production. The regular past tense, formed by adding the regular affix /-d/ to the verb stem [as in jump-jumped; agree-agreed], is the paradigmatic example of a predictable, rule-like process. The irregular past tense, applying to a closed set of about 160 English verbs, represents the converse case of an unpredictable and idiosyncratic process [as in think-thought; make-made], requiring rote learning of each example.

This debate has taken a strongly neuropsychological turn over the past five years, with the publication of several sets of results which point to the underlying dissociability of the neural systems required for the successful production and perception of regular and irregular inflected forms. The pattern that emerges links particular patterns of neuropathology to selective deficits with either type of material. Deficits for the irregulars are associated with damage to L temporal cortex whereas deficits for the regulars are associated with damage to L inferior frontal cortex (LIFC) and underlying structures. The association of lesion site and behavioural deficit suggests that the LIFC is preferentially involved in processing regular inflectional morphology, and supports specialised mechanisms for handling morpho-phonologically complex forms, such as the English past tense (Marslen-Wilson & Tyler, 1997; 1998; Tyler, Randall, & Marslen-Wilson, 2002a; Tyler, deMornay-Davies, Anokinah, Longworth, Randall, & Marslen-Wilson, 2002b).

These claims have not, however, gone unchallenged, and both theoretical and empirical arguments have been adduced to support the contrary, single systems view. Joanisse & Seidenberg (1999) have proposed a unitary computational model in which deficits involving the irregulars reflect damage to semantic systems, while deficits involving the regulars reflect a phonological deficit. Correlational evidence to support this is provided by Patterson, Lambon Ralph, Hodges, & McClelland (2001), showing that patients with a progressive semantic disorder perform less well with irregular forms, while non-fluent aphasics with associated phonological deficits perform less well on the regular forms (Bird, Lambon Ralph, Seidenberg, McClelland, & Patterson, in press). The weight of the current evidence, however, as summarised below, suggests that some degree of underlying dissociation is nonetheless the correct analysis.

L2.2.1 Semantics and the irregular past tense

Marslen-Wilson & Tyler (1997, 1998) were the first to report a correlation between semantic deficits and impaired performance on the English irregular past tense. In an auditory-auditory repetition priming task, two patients with impaired semantic priming (for pairs like cello/violin) showed preserved priming between regular past tense pairs (jumped/jump) but impaired priming for irregular pairs (gave/give). We moved in two directions to evaluate the implications of this result.

In a continuing programme of collaborative research with Tyler (CSL, Cambridge), we probed in more detail the patterns of neuropathology associated with dissociations in performance on the regular and irregular past tense morphology, and their association with semantic impairments (Tyler et al, 2000b). We tested five nonfluent patients, all of whom had extensive LH damage involving L inferior frontal gyrus and underlying structures, and four Herpes Simplex Encephalitis (HSE) patients with semantic deficits who had damage to inferior temporal cortex but where inferior frontal cortex was spared. In a new priming study, extending and replicating the earlier work (Marslen-Wilson & Tyler, 1997), the nonfluent patients showed no priming for the regular past tense but significant priming for the irregulars (whereas controls show priming for both). In contrast, the HSE patients showed significantly impaired performance for the irregulars in an elicitation task (Tyler et al, 2000b). The linkage of distinct patterns of behavioural deficit with disjoint patterns of neuropathology suggest that two separable systems underlie processing of the regular and irregular past tense.

A second set of experiments confronted more directly the implied causal relationship between semantic impairment and deficits with the irregulars, asking whether the underlying relationship between irregular forms and their stems was semantic rather than linguistic and morphological. Two studies with normal adults suggested, however, that the relationship is morphological in both cases – i.e., that gave and give are related because they share a common morpheme, in the same way as jumped and jump, and in contrast to semantically related pairs, such as cello/violin, which do not have a morpheme in common and are lexically quite separate. In a delayed repetition priming experiment, designed to separate semantic effects from morphological effects, priming of regular and irregular pairs is equally well preserved, while semantic priming has dissipated (Marslen-Wilson & Tyler, 1998). In an ERP study, conducted in collaboration with Mark Johnson and Gergo Csibra (Birkbeck, London), we evaluated the patterns of brain activity associated with regular, irregular, and semantic immediate cross-modal priming. The results were unequivocal, with regular and irregular priming patterning together, and both showing left anterior negativities standardly associated with linguistic processing, while semantic primes showed only a centrally distributed N400-type effect (Marslen-Wilson, Csibra, Ford, Hatzakis, Gaskell, & Johnson, 2000). On the basis of these two studies, we interpreted the co-occurrence of semantic deficits and of disrupted access to irregular past tense forms as reflecting a shared dependence on lexical access processes that mediated access to stored whole forms, but not as reflecting a causal relationship between damage to semantic systems and impaired performance on irregular forms.

L2.2.2 Phonology and the regular past tense

The account that we have developed of the English regular past tense attributes the impairment in patients with left inferior frontal damage to specific difficulties with morpho-phonological parsing – i.e., with the segmentation of complex inflected forms, such as the regular past tense, into its morphemic components. The single mechanism account (Joannisse & Seidenberg, 1999) argues that a general phonological processing deficit causes the poor performance with the regular past tense, and does not recognise the possibility of a deficit specific to morpho-phonological parsing. To evaluate the claims made by these different approaches, we developed a speeded same-different judgement task for use with four nonfluent patients with documented difficulties with the regular past tense (Tyler et al, 2002a). We compared patients' ability to detect the difference between the past tense and stem of regular (played/play) and irregular (taught/teach) past tense verbs, as well as matched pseudo-regular and irregular pairs (trade/tray and port/peach). These real word conditions were accompanied by matched sets of non-words. Patients' latencies to the regular past tense real word-pairs were consistently slower than to the phonologically matched pseudo-regular and non-word pairs. To test for a general phonological processing deficit, we conducted several tests of phonological processing ability. The results show that the patients had a range of difficulties in phonological processing, from very mild to severe, which did not correlate with their performance on the speeded judgement task. This pattern of results is inconsistent with the Joannisse & Seidenberg analysis, and supports a specialised morpho-phonological processing mechanism which can be dissociated from other phonological processes and which is used directly in the processing of the regular past tense.

The differential difficulty of the non-fluent patients with the regular past tense comparisons leads to predictions for the performance of unimpaired subjects in neuro-imaging experiments with the same materials. We have begun to evaluate these predictions in fMRI studies, using a sparse imaging technique to allow the test-pairs to be presented free of interference from scanner noise (Tyler, Stamatakis, Post, Randall, & Marslen-Wilson, submitted). Interestingly, activation patterns for the regular past tense comparisons differ from the control conditions in a set of areas that overlap closely with brain areas that are damaged in the patient population – these include left superior temporal and left inferior frontal cortex, and the anterior cingulate. This points to a fronto-temporal network, where temporal lobe lexical access processes may be modulated by specialised frontal systems activated by morpho-phonologically complex input strings.

L2.2.3 Regularity and irregularity in cross-linguistic perspective

The analysis we have developed of the regular/irregular contrast in English focuses on the contrast between the irregular past tenses as phonologically simple forms, that can access stored lexical representations directly, while the regular past tenses, because they are morpho-phonologically complex combinations of stems and affixes, require the involvement of further analysis processes. However, this association of regularity and irregularity with the presence or absence of morpho-phonological complexity, is a historical accident that is specific to English (and perhaps to Germanic – see Clahsen, 1999). In other languages, it is typically the case that both regular and irregular forms require the application of morpho-phonological parsing mechanisms. This predicts that we should not see the same differentiation between regular and irregular forms, in selected processing tasks, that we see in English. Specifically, in cross-modal immediate repetition priming in English (e.g., Marslen-Wilson, Hare, & Older, 1993), we consistently find that irregular past tense forms do not prime their stems (as in gave/give) while strong priming is obtained for regular past tense pairs (as in jumped/jump) . In an earlier study (Orsolini & Marslen-Wilson, 1997),we tested this prediction for Italian, where both regular forms (e.g, prendiamo "we take" from the verb prendere) and irregular forms (such as presero "they took", also from prendere) are morpho-phonologically complex, being composed of a verb stem and one or more inflectional affixes, and where we found equally strong priming for both regular and irregular pairs. We have now extended this to two further languages.

The French language allows a wider range of contrasts than Italian in types of regularity of verbal inflection. As in the English and the Italian studies the subjects heard a spoken prime (such as aimons, 'we love') immediately followed by lexical decision to a visual probe (such as aimer, 'to love'). We contrasted four types of French verbs, varying in the phonological and morphological regularity of their verb form inflection, and ranging from fully regular verbs (aimons/aimer, 'we love/to love) to entirely irregular verbs with idiosyncratic stem alternations (irons/aller, 'we will go/to go'). Even for an alternation like irons/aller, where the irregular stem {ir-} has no phonological relationship to the base form of the verb, the surface form is still morpho-phonologically complex, being made up of the irregular stem plus the regular inflectional affix {-ons}. This marks the first person plural in the same way as in regular forms such as aimons. Morphologically related primes, whether regular or irregular, significantly facilitated lexical decision responses for all verb classes. The same pattern of results was observed in a second experiment using a masked priming paradigm (Meunier & Marslen-Wilson, 2001; in press). These results contrasted with English, where regularly inflected verbs prime their stems but irregular verbs do not. A comparable pattern was also observed for Polish, which allows for extensive contrasts in regularity and irregularity in word formation, both for verbs and for nouns (Reid & Marslen-Wilson, 2001).

These cross-linguistic results are consistent with our basic hypotheses about regularity and irregularity effects in the English past tense, although they need to be evaluated further in appropriate neuropsychological populations (planned research with Polish aphasics is discussed in SL3). The regular/irregular contrast in English does indeed tap into separable underlying processing mechanisms, but only because this contrast, in English, is confounded with morpho-phonological complexity.

L.2.2.4 Cross-linguistic contrasts in morpheme frequency effects; computational and empirical studies

An important theoretical distinction in models of spoken and written language processing is between localist models (e.g., Shortlist, Norris, 1994) and distributed models (such as the DCM; see L1.3.2). An increasingly prominent domain for evaluating these contrasts is the representation and processing of inflectional and derivational morphology (e.g. Plaut & Gonnerman, 2000). A relevant source of evidence here is the effect of word and morpheme frequency on the recognition of morphologically complex words. Previous experimental work in Dutch (Baayen, Dijkstra & Schreuder, 1997) has been argued to be consistent only with a dual-route, localist model in which inflected words are both stored as whole forms and are decomposed into stems and affixes. In recent work, we have developed a distributed connectionist model that can recognise Dutch nouns and verbs in both monomorphemic and inflected forms (Davis, van Casteren & Marslen-Wilson, in press). When tested on a lexical decision task, the network shows the appropriate pattern of frequency effects to simulate experimental data from Dutch, but only when homonymous affixes are included in the training set - such as the Dutch plural affix {-en} which also marks verb infinitives. Competition from the homonymous forms of an inflectional affix means that effects of word-form frequency are more robust for items that are marked with an inflectional affix which serves two distinct morphological functions.

In recent experimental work we have tested the predictions of this distributed processing model when applied to English inflected forms. In an experiment comparing the comparative {-er} and superlative {-est} adjectival endings (Ford, Davis & Marslen-Wilson, in press), we observed significant differences in the processing of these two inflected forms. Items that ended in the homonymous {-er} affix (which is also used for agentive forms like dancer) were processed more slowly, and did not differ in their behaviour from items matched on word-form frequency. We have also explored effects of affix homonymy in the processing of the English {-s} plural ending, which also marks the third person singular form of verbs. Results show stronger effects of lemma frequency than observed in Dutch, suggesting that processing of the English plural is less affected by competition from the verbal inflection. This finding may reflect cross-linguistic differences in the relative frequency of verbal interpretations of the noun plural ending. Further simulations are currently under way to simulate these differences using the distributed model we applied previously to Dutch (Davis et al, in press).

L2.2.5 Electrophysiological indicators of morphological processing

Research has also begun using EEG techniques to probe potential differences in the cortical signatures of stems and inflectional affixes, using the Mismatch Negativity response (MMN – for further details see reports under L4). In a first study addressing this issue we compared the MMN to a verb stem to that elicited by an inflectional affix. The results indicated (a) an earlier MMN to the stem as compared with the suffix and (b) a more frontal distribution of the verb stem-elicited MMN and a more posterior distribution of the suffix-related MMN (Shtyrov & Pulvermüller, 2002a). Distributed source estimates localized the main sources of the verb MMN in inferior frontal cortex and of the suffix MMN in posterior perisylvian and parietal areas. This is consistent with earlier claims that function words and inflectional affixes have a left perisylvian neuronal representation (Pulvermüller, 1995; Pulvermüller, Lutzenberger, & Birbaumer, 1995). Several further experiments are planned to try to unpack these phenomena in more detail (see future proposals in SL3 and SL4)

Additional research is in its preliminary stages, again using MMN techniques, to probe the representation of regular and irregular verb forms in English, and the representation of consonantal roots and word patterns in Arabic (see SL3).

Project L3/M4: Short-term memory and speech perception

Scientific direction: Norris (50%), Page (100%)

MRC Research support: Hall (100%), Woods (50%)

External grant support: Cumming (50%)

Student: Cumming (100%)

The study of short-term memory (STM) and the study of language comprehension have effectively been treated as two quite independent topics of research in cognitive psychology. However, almost all memory researchers believe that STM must play some role in language processing, and there is little doubt that speech recognition and comprehension are reliant on some form of temporary storage. This project was designed as an initial step toward developing an integrated account of the relation between STM and language. The work focussed on two of the most significant links between memory and language; both require the maintenance of representations of order (e.g. of phonemes or words), and both depend on the storage or manipulation of phonological representations. The main emphasis of this project was computational modelling, supported by empirical work to place additional constraints on theoretical development. At the time this project began, there were already well established computational models of speech recognition (e.g. TRACE, Shortlist). In contrast, there had been very little work developing computational models of STM. The research reported here therefore started from the view that any attempt to provide an integrated account of STM and language needed to begin by developing a computational model of STM. In particular, we needed to focus on modelling memory for ordered representations of phonological information.

L3.1 Computational modelling of short-term memory: The Primacy and the SEM models

The most significant achievement of this project over the last report period has been the development of two new computational models of short-term memory (STM): the Primacy model (Page and Norris, 1998) and the Start-End Model (SEM) (Henson, 1998). The Primacy model can be considered to be a computational implementation of the phonological loop component of the Working Memory model of Baddeley and Hitch (1974). The SEM model deals with serial recall at a more general level and includes features designed to explain memory over longer periods than normally supported by the phonological store.

Both of these models were designed to address shortcomings in existing models of STM. Although the Working Memory model has been exceptionally productive, and successfully accounts for much of the central data on STM, it remains limited by the fact that it is a qualitative verbal theory. The primary source of data on STM comes from the immediate serial recall task, yet the Working Memory model has no account of how information from memory can be recalled in the correct order. We took the view that further progress in the field of STM research was dependent on the development of computational theories that would provide quantitative simulations of the data.

An initial limitation on this enterprise was that most of the existing studies in the literature did not describe their data in sufficient detail to provide the necessary insights for modelling. Most reports of STM data simply report serial position curves, but many only report proportions of items or lists correctly recalled. One of our initial tasks was therefore to collect data that could be analysed in greater detail. Some of this work is reported in Henson's thesis, along with procedures for analysis of serial recall data. At the outset of this work we realised that one of the most important constraints on models of STM was data reported by Baddeley (1968). Baddeley found that when subjects were presented with lists with an alternating pattern of phonologically confusable or non-confusable items (e.g. BFDLCY) recall of non-confusable items was unaffected by the presence of the confusable items in the list. This finding, since replicated and extended by Henson, Norris, Page and Baddeley, (1996), has come to be a benchmark test of models of STM. Although other models can provide qualitative simulations of these data, only the Primacy model and SEM can give accurate quantitative simulations. In particular, this data appears completely incompatible with models based on associative chaining. Chaining models must predict that if one of the confusable items (say D) is not recalled, then that item will not be available as a cue for the recall of the following non-confusable item (L). Any increase in errors on confusable items must therefore also increase errors on non-confusable items. Also, this data can only be explained by models using a two-stage recall process, as first proposed in the Primacy model.

The central assumption of the Primacy model is that order is represented by the relative activation levels of list items. The first item in a list is assigned a particular level of activation, and successive items each have activation levels that are lower than the previous activation by some constant amount. Recall is modelled as a noisy choice process, followed by item suppression. That is, zero-mean gaussian noise is added to all item activations and the most strongly activated item is then selected for recall. The activation of that item is then suppressed so that it can not be recalled again. Errors in recall occur because the noise in the selection process can lead to the selection of items in the wrong order. As activations decay, the difference in activation levels between nearby items decreases, and so the possibility of selecting the wrong item increases. Performance therefore declines over the course of the list (the primacy effect). Performance improves for the last item in the list (recency) because that item can only be recalled in the wrong position by being recalled too early. Other list items can be recalled either too early or too late. With some additional assumptions about the nature of the rehearsal process, the model gives very precise simulations of the central characteristics of STM. An additional component of the model is influenced by the phonological relationship between list items, and causes the degradation in performance seen with lists of phonologically similar items (BVPDE etc). The full model can simulate data (Baddeley 1968; Henson, Norris, Page and Baddeley, 1996) that cannot be accurately simulated by any model other than SEM, which incorporated the same assumptions about the mechanism of retrieval from phonological memory. The only other model that can simulate the general pattern of the data is the latest version of the Burgess and Hitch (1999) model. Page and Norris (1998b) have also presented a connectionist implementation of the Primacy model designed to highlight the parallels between recall from STM and models of speech production.

The SEM model is rather more complex than the Primacy model. Whereas the primacy model relies on an activation gradient that decays over the course of a list, the SEM also has a second signal that rises over the course of the list. These two signals provide a two-dimensional retrieval cue. Effectively, this cue codes position relative to the start and ends of the list. Henson (1999) contrasted the predictions of the SEM model with those of positional models by examining protrusion errors in serial recall. Subjects often make errors where an item from the previous list is recalled in the current list. These items frequently appear in the same position as they did in the earlier list. Henson showed that there were frequent protrusions from the end of one list to the end of the next list, even when the lists varied in length. This is to be expected from the SEM model, but is inconsistent with models using position-item associations, where the final items in lists of different lengths would have different positional associations.

Note that the Primacy model was designed specifically as a model of the phonological loop, and between list protrusions operate over time-spans well beyond the duration of the loop. These positional protrusions therefore don't have any implications for our understanding of the loop. However, Page and Henson (2001) have suggested that the Primacy and SEM models might be combined to provide an integrated account of memory for serial order over both the short and medium term.

The data from Henson et al (1996) raised considerable doubt over the plausibility of chaining models. In work originating from Cumming's thesis we turned our attention to an evaluation of positional models. In this research we used the Hebb effect (Hebb, 1961), whereby subjects performance in immediate serial recall improves on a list which is repeated every three or so trials. The representation of the repeating list that is being built up can be probed by presenting a 'transfer' lists that differs in some systematic way from the repeated Hebb list. Cumming, Page and Norris (in press) used transfer lists where alternate list items were identical to the items used in the repeated Hebb lists, while the order of the remaining items was rearranged (e.g. 542716983 - > 643792581, where items in even numbered positions remain unchanged). Contrary to the predictions of theories depending on associations between items and their positions (e.g. Burgess and Hitch, 1992,1999; Brown, Preece and Hulme, 2000), there was no benefit to the transfer lists over control lists consisting of a completely reordered set of items. Although it has been suggested that one of the advantages of positional models is that the build up of position-item associations over time could account for the Hebb effect, these results show that the Hebb effect is not due to position-item associations. Also, Cumming et al. presented simulations using the Burgess and Hitch model to show that it did not simulate the basic Hebb effect after all.

L3.2 Effects of irrelevant speech on STM

Another project has investigated the effects of irrelevant speech on short-term retention of visually presented lists. When participants in an ISR task are presented with speech that they do not have to attend to, their memory performance deteriorates (Colle and Welsh, 1976; Salame and Baddeley, 1982, 1986). Several theories of STM make quite specific claims about the underlying mechanism of the irrelevant speech effect. For example, the Object-Oriented Episodic Record (OOER) theory of Jones (1993) predicts that irrelevant speech can only effect performance if is occurs during rehearsal. Nairne's (1990) feature theory has to predict that the irrelevant speech must be presented at the same time as the stimulus list. In a series of studies (Norris, Page and Baddeley, submitted) we have shown that irrelevant speech still impairs performance even when presented after the end of the stimulus list, during an interval in which subjects are prevented from rehearsal by shadowing digits presented at a rate of one every 500ms. Furthermore, there is no significant retroactive irrelevant speech if subjects perform articulatory suppression during list presentation so as to prevent the visual material being recoded into the phonological loop. The effect therefore appears to depend specifically on information being retained in the loop. The complete pattern of data is inconsistent with both Nairne's feature model, and Jones OOER model, but is consistent with the Working Memory model and, by implication, computational models such and the Primacy model and Burgess and Hitch's position-item model.

Note that all of the computational modelling reported here, and the modelling of spoken word recognition in Shortlist and Merge (L1.3.2) uses localist connectionist models. Page (2000a, 2000b) has recently published an influential Behavioral and Brain Sciences article comparing the merits of localist and distributed representations. In that paper he presents a strong case that localist models are to be preferred over distributed models, both for theoretical reasons, and for their greater consistency with the neurobiological data.

A further series of experiments, still in progress has been investigating several somewhat anomalous results in the STM literature that do not fit neatly into the standard Working Memory model. For example, there are suggestions that the phonological similarity effect is much more long lasting with auditory than visual presentation (Longoni, Richardson, & Aiello, 1993). This would suggest that the similarity effect is not simply dependent on a phonological store that can be driven by visual or auditory input, but also has an acoustic/phonetic component too. We have confirmed and extended this result in more carefully controlled studies comparing the time-course of the phonological similarity effect with visual or auditory presentation. Other work has investigated the question of whether articulatory suppression really does prevent phonological recoding of visually presented material, as assumed in the Working Memory framework. Although suppression consistently eliminates the phonological similarity effect for visual, but not auditory, lists, subjects can nevertheless judge whether two visually presented words are homophones, even when suppressing. This implies that they do have access to phonological representations. We have combined the serial recall task and a homophone judgement task by requiring subjects to detect homophones in a list of words which they have to recall in order. When the homophones appear in adjacent list positions, subjects can perform this task reliably, even when suppressing. Performance declines rapidly when one or two items intervene between the homophones, This suggests that some access to phonological representations is possible in a serial recall task, but this information is only available very briefly. Further work is investigating whether forcing subjects to attend to phonology, by requiring them to perform a homophone detection task, can modulate the phonological similarity effect, both with and without suppression.

In summary, the theoretical work reported here has resulted in the development of two new computational models of short-term memory while the empirical work has generated data that places considerable constraints on the form that any successful model of STM must take. Data from Henson et al (1996) allows us to eliminate a whole class of theories based on associative chaining. Cumming et al (in press) presented data inconsistent with position-item theories. Finally, data on irrelevant speech reported in Norris et al (submitted) poses considerable problems for the feature integration theory (Nairne, 1990; Neath, 2000) and the OOER theory of Jones (1993).

Project L4: Neurophysiology of Language

Scientific Direction: Pulvermüller (90%)

MRC-scientist support: Shtyrov (90%), Hauk (90%)

Student: Harris (100%)

The MRC Cognition and Brain Sciences Unit's project L4 on the neurophysiology of language started with the appointment of Friedemann Pulvermüller in summer 2000, and subsequent appointments of Olaf Hauk and Yury Shtyrov later in the same year. In January 2001, a new 64-channel EEG system was up and running in the newly converted CBU EEG laboratory. Our research currently focuses on methods with high temporal resolution, in particular magnetoencephalography (MEG) and electroencephalography (EEG), to reveal the exact time-course of cortical activity when words and sentences are being processed. Time course information is particularly important in the investigation of language, because language comprehension is a dynamic process in which various types of information (phonological, syntactic, semantic etc.) are being integrated within a fraction of a second. Compared with fMRI, the EEG and MEG methods allow for less precise conclusions on where in the brain activity arises. The future strategy is therefore to complement the exact temporal information provided by EEG and MEG results with data obtained with techniques allowing for precise localization, in particular functional Magnetic Resonance Tomography (fMRI) and Transcranial Magnetic Stimulation (TMS).

The research reported here is framed within a neural model of language function that uses established neuroscientific principles to model language-related spatio-temporal patterns of brain activity. The model aims to spell out phonemes, words, sentences, and their meaning in terms of concrete neuron circuits, taking as a starting-point the concept of Hebbian cell assemblies. These are neuronal networks that form as a consequence of correlation learning in a biological associative memory, the cortex (Pulvermüller, 1999). From a clinical perspective, we hope to convert knowledge about the neurobiological basis of language into concrete proposals for clinical practice, with the aim is of developing and testing scientifically-based treatment approaches for acquired language deficits following brain lesion.

L4.1 Neurophysiological activity reflecting word-category-specific processes

A prediction of a neurobiological model of word processing in the brain is that words referring to actions are cortically realized by distributed neuronal ensembles that include neurons related to the execution of the relevant motor programs (Pulvermüller, 2001). A word such as "(to) kick" should be realized not only by neurons housed in the perisylvian language areas related to the articulation and acoustic perception of the word, but its neuronal representation should incorporate additional neurons involved in the coordination of the movements involved in actual kicking. This is a necessary postulate for any neurobiological language model that takes seriously the principle of association learning. If neurons that frequently fire together also wire together by strengthening their synaptic connections, the disjoint neuronal populations related to the word form and the referent actions should link into a strongly connected neuronal group when word and action frequently occur at the same time or in close temporal succession. The argument made for the leg-related word "(to) kick" can be extended to other action words, for examples hand/arm-related words, such as "(to) pick", and face-related words, such as "(to) lick". These considerations suggest that action words of different types are cortically realized as cell assemblies with different cortical distributions. It is well-known that the motor and premotor cortices in the frontal lobe are organized topographically with the leg representation located dorsal to the arm representation, which, in turn, is dorsal to the representation of the face (He, Dum, & Strick, 1993; Penfield & Rasmussen, 1950). Therefore, the word-related neuron ensembles should be differentially distributed over fronto-central areas (Pulvermüller, 2001). Allthough all word networks would include neurons in the perisylvian language areas, the leg-related words would accordingly be realized as networks that include additional neurons in dorso-medial primary motor and pre-motor areas, hand/arm-word representations would include more inferior action-related neurons, and face word representations neurons in inferior fronto-central areas. The referent actions of action words would be woven into the word-related neuronal ensemble (Pulvermüller, 2001).

According to classical neurological models of language, words are processed in two restricted language centers in the dominant hemisphere, usually the left in right-handers. Modern brain imaging studies, however, showed that various other areas can also become active during word processing. Retrieving word meaning, for example, certainly involves additional areas, although there is, at present, much discussion about their exact definition (for an overview, see Pulvermüller, 1999). Category-specific patterns of brain activity have been found in numerous neurophysiological and metabolic imaging studies (for an overview, see Pulvermüller, 2001), although not all studies have observed category differences over varying tasks and stimulus sets (Devlin et al., 2002). In our recent neurophysiological studies, we found consistently that well-matched words from different categories (function vs. content words, nouns vs. verbs, visually-associated vs. action associated nouns) led to distinct patterns of cortical activation, and that the neurophysiological differences are best explained by semantic differences between word types (Pulvermüller, Assadollahi, & Elbert, 2001; Pulvermüller, Härle, & Hummel, 2000; Pulvermüller, Lutzenberger, & Preissl, 1999; Pulvermüller, Mohr, & Schleichert, 1999).

L4.1.1 Behavioral and EEG studies of action semantics

In behavioral and neurophysiological experiments, we tested the predictions, outlined above, arising from a Hebbian model of word processing. Because the predictions relate associations at the cognitive level (for example, whether a word refers to, and reminds one of, actions performed with the leg) to neurophysiological events in the brain, it was necessary to establish the cognitive properties of the stimulus words used in the neuroimaging studies. This is only possible in behavioural experiments. We asked subjects to judge words in English and in German (in separate studies) with regard to their action associations. The ratings allowed us to pick groups of words primarily associated with one of the three body parts under examination, face, arm/hand, and leg/foot. The words were matched for physical and psycholinguistic variables, such as length, familiarity, word frequency, and imageability. This led to well-matched stimulus groups, which significantly differed in their action associations (face, arm, and leg words). These were used in subsequent imaging studies.

In neurophysiological studies, the EEG was recorded while subjects made lexical decision responses to words shown briefly at fixation. Response times were slightly slower for leg words as compared with the other two word categories. Importantly, event-related brain potentials reliably differed between subcategories of action words. As Current Source Density Analyses (CSDA) indicated, leg words elicited stronger activity (as indicated by stronger outward flow of electrons) at the top of the head, near the cortical representation of the leg, as compared with face-related words. Face words, in contrast, produced stronger activity signs at left-anterior sites, close to the cortical representation of the face. Although these data do not allow for an exact localization of the cortical sources of the word-category-related differences in brain activation, the results argue that subcategories of action verbs related to actions performed with different body parts are neurophysiologically distinct (Pulvermüller, Hummel, & Härle, 2001).

In the earlier experiment, subjects had to respond overtly to the stimulus words. Since differences in response times were found between action word subcategories, differential motor preparation is a possible confound. Therefore, we are investigating putative neurophysiological differences between leg- and face-related words with a different set of stimuli and in a silent reading task in which no motor response is required. To obtain a better estimate of the cortical locus of the word category differences in brain activation, Olaf Hauk calculated Minimum Norm Estimates (MNE). The MNE is a method for solving the so-called Inverse Problem (von Helmholtz, 1853) which selects the unique solution that explains the scalp topography by the least amount of overall current (Hämäläinen, Hari, Ilmoniemi, Knuutila, & Lounasmaa, 1993). Our preliminary MNE of the cortical generators indicate that a central dorsal area including the primary motor and premotor areas representing the leg were more strongly activated for leg words as compared with other word groups, and that an inferior frontal area was most active for face words (Hauk & Pulvermüller, 2002). We take these results as evidence that areas in the frontal lobes are differentially activated by words referring to actions performed with different body parts. The plan is to continue this line of research in the future proposal, project SL4.1.

L4.1.2 When is word meaning reflected in the brain response?

The great strength of neurophysiological data is the exact localization of the effects in time. Time-wise, our results were surprising, because several experiments unequivocally demonstrate that word category differences were present early in the brain response. The earliest meaning-related differences (to frequently repeated word stimuli presented in a memory task) were already observed 100 ms after the onset of visual word stimuli (Pulvermüller, Assadollahi et al., 2001). In this MEG study carried out with Ramin Assadollahi and Thomas Elbert at the University of Konstanz, we found a high correlation between the magnitude of an early magnetic brain wave (latency ~100 ms) elicited by matched written words and our subjects' ratings of the strength with which individual words reminded them of referent perceptions and actions. This suggests that meaning-related aspects of a word are reflected in the brain response already 100 ms after the information in the input allows for word identification.

While some studies suggested a very early onset of the neurophysiological differences between word categories, the latest word category differences we saw in our series of experiments were present at ~200 ms after visual word onset (Pulvermüller, Hummel et al., 2001). Clearly, future research is required to exactly define the point in time where specific brain responses possibly related to the meaning of a word arise. Some of the variance may be accounted for by physical word properties, such as the length of written words and their sound structure and recognition point (Marslen-Wilson & Tyler, 1980) of spoken words (see also L2.3 and L4.3).

The fact that the brain distinguishes early between word categories, at ~100-200 ms, after delivery of the information necessary for word identification, may be important for theories of language in the brain. It is consistent with proposals based on psycholinguistic reaction time experiments according to which access to the lexical and semantic information occur early in word processing (Marslen-Wilson & Tyler, 1980). Our findings speak against the view that the meaning of words is accessed only at around 400 ms after the critical information is presented (e.g, Friederici, 2002). Instead, they suggest that meaning access is an early neurophysiological process occurring near-simultaneously with the access to lexical and phonological information. To further clarify these issues, we plan to look more closely at the specific brain activity patterns elicited by different kinds of action words. With the use of advanced neurophysiological source localization techniques (see MR3.2-4), it should become possible to separate the perisylvian phonologically- and lexically-related activity patterns from those in dorsal motor and premotor areas so that conclusions about the spatio-temporal pattern of activation of phonological and semantic activity will become possible.

L4.1.3 Methodological issues in the investigation of word-evoked brain activity

To draw conclusions about the neurophysiological reflections of word semantics (see L4.1 and SL4.1), it is important to study other properties of words that become manifest in the brain response and which therefore can confound the results of EEG/MEG activity related to word processing. Further, as noted, there is the open question of why some of the word category differences surfaced quite early, whereas in other research, they appeared with longer delays (for an overview, see Assadollahi & Pulvermüller, 2001). In a series of studies, we investigated the influence of the factors of word length and word frequency on the EEG and MEG response. In contrast to earlier studies, we kept the variance in length and frequency of our stimuli minimal. This is important methodologically, because variability in these stimulus properties adds noise to the early ERP responses (P70, N100), which are known to be short-lasting and focal, so that potential early physiological category differences may be masked (for discussion, see Pulvermüller, 1999).

A main finding of our studies (Assadollahi & Pulvermüller, 2001; Hauk & Pulvermüller, submitted) is that word length effects became manifest already around 100 ms after word presentation onset, whereas word frequency modulates the neurophysiological brain response slightly later, at ~150 ms. This makes it clear that early neurophysiological differences between words can be related to word length or frequency. However, the differences between long and short and between common and unusual words were always widespread, making it unlikely that topographically specific differences between subcategories of action words (L4.1.1) are a by-product of differences in length or frequency. Nevertheless, due to the modulation of neurophysiological activity related to word length and frequency, it appears advisable in neurophysiological studies of word-category processes to exactly match the word material for these variables. In contrast to earlier studies (King & Kutas, 1998), we could not replicate a correlation of word frequency with the latency of components of the word-evoked neurophysiological response.

In the context of the debate about latencies of word category effects, we note that long words usually elicited relatively large early neurophysiological responses, whereas short words elicited relatively large responses at a later point in time. This indicates that the mixing of long and short words can account for why some investigations found early word-category differences (100-200 ms; Sereno, Rayner & Posner, 1997) and others only found them later (~400 ms; Polich & Donchin, 1987). A similar confound may occur for the variable word frequency. Some of the latency variance found in earlier studies on category-specific word-evoked activity may be accounted for in terms of physical and psycholingusitic stimulus properties.

L4.2 Specific word category deficits after lesions in the right hemisphere

We have proposed that language units are cortically processed by distributed cell assemblies including neurons in both hemispheres, transcortical cell assemblies (TCA, Mohr et al., 1994; Pulvermüller & Mohr, 1996; see also L4.4). These neurons may be left-lateralized in most individuals in the sense that they include more left- than right-hemispheric neurons, but the networks crucial for processing a word would still bridge the midline. The claim is based on associative memory theory and the fact that the perception of a spoken language unit, for example a word, always leads to correlated activity in both cortical hemispheres. To test the TCA model, we can look at the effect of focal lesions in the hemisphere not dominant for language.The TCA model suggests that a right hemispheric lesion can lead to similar, although less pronounced, category-specific deficits to those reported earlier following lesions to the left dominant hemisphere.

Category-specific deficits arising from lesions in the dominant hemisphere are well-known (Warrington & McCarthy, 1983; Warrington & Shallice, 1984). Lesions in the left temporal lobe are sometimes associated with selective difficulties in processing particular word categories, e.g. animal names, whereas left frontal lesions in many cases impair the processing of action verbs (Daniele et al., 1994). Together with Bettina Neininger, doctorate student at the University of Konstanz, Germany, we investigated whether focal lesions in the right non-dominant hemisphere can also lead to selective difficulties in processing particular types of words.

No overt language dysfunction was found in our population of 18 patients with focal ischemic lesions primarily affecting the right frontal or temporal lobes. Consistent with the model, however, a sensitive psycholinguistic test, a lexical decision task, revealed a double dissociation between word groups. Processing of action verbs was imparied after right-frontal lesions, whereas the processing of nouns primarily characterized by visual associations was degraded after lesion in right temporo-occipital areas (Neininger & Pulvermüller, in press). Neurological control patients did not show similar deficits, nor was there any impairment of the processing of nouns characterized by both strong action and visual associations. It was striking that that small focal lesions, for example in primary and premotor cortex, could lead to a marked behavioral impairment that showed up on the lexical decision task (Neininger & Pulvermüller, 2001). This supports the idea that the neuron networks necessary for word processing have a right-hemispheric component as well.

We plan to follow up on this work by searching for other word-category deficits accompanying specific focal right-hemispheric lesions. In this context, we will use TMS to cause temporary modification of the function of different right-hemispheric areas. The effect of such temporary functional modulation will be looked at with psycholinguistic experiments and the results will be used to further evaluate the TCA model (see future proposal SL4.2).

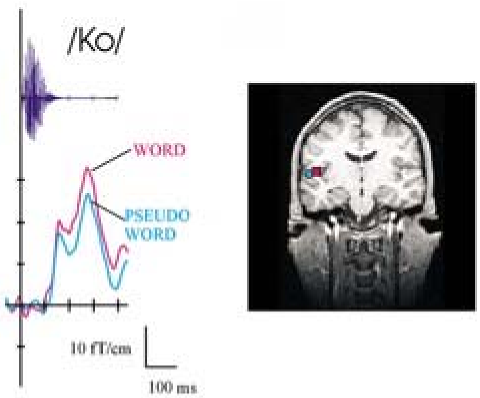
L4.3 The Mismatch Negativity (MMN) as a tool for investigating language in the brain (Friedemann Pulvermüller and Yury Shtyrov, with Risto Ilmoniemi and Risto Näätänen, University of Helsinki)

The neural systems underlying language function are usually explored in the context of tasks where language stimuli are presented and subjects have to focus their attention on these stimuli and perform a linguistic task. Neurobiological models of word processing and language would suggest that strongly linked networks of neurons are built up that specialize in the detection (and production) of words, or sequences of words, and that the strong neuronal connections defining these neuron ensembles lead to spreading of neuronal activity in the network. This should take place regardless of whether the brain is in an attentive or non-attentive state, and regardless of whether attention is directed toward the language input or some other input. A series of experiments has been performed to explore brain processes triggered by language stimuli when these are not the focus of the subjects' attention.

When words are being presented visually, there is, on the one hand, evidence for implicit word processing (Price, Wise, & Frackowiak, 1996), but, on the other, inattentional blindness for words (Rees, Russell, Frith, & Driver, 1999) has been reported when subjects were instructed to engage in a distracting task. Since, from both ontogenetic and a phylogenetic perspectives spoken language is more basic than written language, we used spoken words and word sequences for our investigations.

The Mismatch Negativity (MMN), a neurophysiological index of the detection of a change in the acoustic environment that can be elicited in the absence of focussed attention (Näätänen, 2001) was recorded to spoken CV syllables. Subjects were instructed to watch a simultaneously presented silent video film and ignore the acoustic stimuli. The critical syllables followed context syllables with which they formed either words or meaningless pseudo-words. The MMN was significantly altered by the context. The same syllable elicited larger MMNs when it terminated a real Finnish word than when it was presented in pseudo-word context (Pulvermüller, Kujala et al., 2001). Further experiments ruled out the possibility that the MMN enhancement to words is due to bi- or trigram frequencies of the phonemes making up the words (Pulvermüller, Kujala et al., 2001). We call this enhancement of the MMN in word context relative to pseudo-word context the lexical enhancement of the MMN (see Figure L3 below). These results show that word-related brain responses can be elicited when subjects do not focus their attention on the language input. The activation of the memory traces for words does not appear to require that subjects engage in a linguistic task.

Figure L3: Words elicited larger magnetic MMNs than pseudowords (left side). This lexical enhancement effect was present at ~150 ms after the stimulus information necessary for word recognition. The locus of the main cortical source, as revealed by calculating the Equivalent Current Dipole, was found in the left superior temporal cortex. Source locus did not distinguish between words and pseudowords. From Pulvermüller, Kujala et al., 2001).

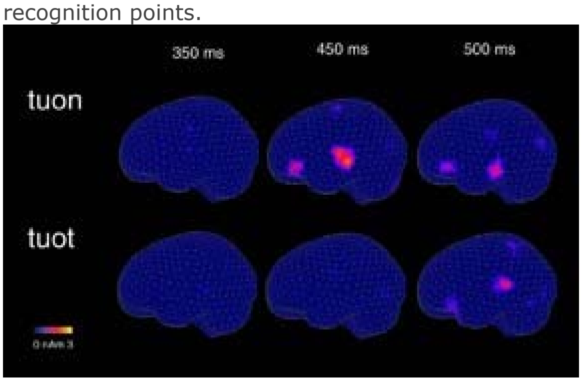


The lexical enhancement effect was originally obtained with Finnish stimuli, and we have since replicated this with English stimuli (Shtyrov & Pulvermüller, 2002b). In a study using monosyllabic English words, deviant and standard CVC stimuli were distinguished by their final phoneme. Word-word and word-pseudoword pairs were included, as in pairs like type-tight and pipe-pite. An item ending in a [t] was always used as the frequent standard stimulus, whereas an item terminating with a [p] was the infrequent deviant stimulus that elicits the MMN. Physical differences between stimuli were minimized by cross-splicing word-initial CV syllables and word-final phoneme sounds so that all standard stimuli shared their final sound and the same was true for the deviants. The unexpected word-final phoneme elicited a larger MMN than the same phonetic signal terminating a CVC pseudoword, thereby replicating a lexical enhancement effect for the English words. An additional result was that the enhancement effect was dependent on the lexical status of the deviant stimulus but not of the standard stimulus (Shtyrov & Pulvermüller, 2002b).

In more recent research (Pulvermüller, Shtyrov, Ilmoniemi, & Marslen-Wilson, submitted) we have even more direct evidence for the sensitivity of the MMN to linguistically and cognitively relevant processing events. The concept of "word-recognition point" is well established in the Cohort Model of Marslen-Wilson, and claims that spoken words can be identified by the listener as soon as the speech input diverges from other possible words in the language. Thus, for example, the fragment "crocod…" might be sufficient to identify the word crocodile, and the recognition point would be set in the region of the /d/. In experiments run in Finnish, and again using the MEG laboratory in Helsinki, we were able to measure the magnetic Mismatch Negativity (MMN) elicited by spoken words, for pairs of words like tuon and tuot. These are forms of the verb tuo 'bring', with either the inflectional ending [-n], meaning "I bring" or with the ending [-t], meaning "you bring". The participants were independently tested to determine their individual recognition points for these pairs, with recognition point being consistently slower for tuot. In the MMN experiment itself, the two words alternated as standard and deviant across conditions.

The results were striking, with the latency and detailed timing of the MMN responses primarily determined by word recognition points (see Figure L4 below). Both ECD (Equivalent Current Dipole) and MCE (Minimum-Norm Current Estimate) calculations of the spatio-temporal properties of the MMN responses showed (a) that these peaks occurred about 100-150 ms after the information in the acoustic input was sufficient for word recognition, and (b) that the peak was significantly delayed for the word (tuot) with a later recognition point. The neural generators for these responses were located in the left superior temporal cortex, which is known to play a role in mapping sound onto lexical meaning. Even more telling was the further result that the recognition-points computed in the gating task for the individual participants correlated significantly (r = 0.66) with the latency of these activity peaks in superior temporal cortex. We conclude that the latency of the magnetic MMN elicited by spoken words reflects an early brain process that underlies the recognition of individual lexical items in individual subjects.

Figure L4. Minimum Current Estimates of cortical sources activated during the presentation of the spoken Finnish words "tuon" and "tuot". Gating experiments revealed average word recognition points for "tuon" at 350 ms and for tuot at 420 ms after word onset. Starting at ~100 ms after the respective recognition points, cortical activation was observed in the left superior temporal lobe, correlated in time with individual subject's recognition points.



This is not only an important result in itself, but also it validates the use of the MMN to probe the higher-level structure of language processing mechanisms in the brain. In future research, we plan to exploit this vigorously, using the MMN to examine more generally the spatio-temporal patterns of cortical activation invoked by linguistic material (see SL3 and SL4 in the future proposal).

L4.4 Constraint-induced aphasia therapy

Scientific development needs to contribute to clinical practice. This project addresses a specific clinical domain where neuroscientific theories of language can potentially become useful, namely aphasia therapy. On this basis we have developed and tested a new aphasia therapy method, called Constraint-Induced Aphasia (CIA) therapy. The principles underlying CIA therapy are (i) to provoke a high correlation of neuronal activity patterns by using a massed practice regime, (ii) to stimulate distributed cortical systems related to the processing of words and their meaning by providing behaviorally relevant multimodal input that mimicks communication in everyday life, and (iii) to prevent the learned nonuse of cortical functions that is frequently observed in individuals suffering from stroke by introducing communication contraints (Taub, Uswatte & Elbert, 2002).

In a randomized and controlled study, we could show that Constraint-Induced Aphasia therapy leads to significant improvements of language performance in chronic aphasics over a period of 10 days of intense treatment (Pulvermüller, Neininger et al., 2001). Comparable improvement was absent in a control group receiving the same amount of conventional language treatment. Changes of language-related brain activation in the course of language therapy were documented using event-related potentials.

We plan to extend this research by looking at the plastic changes related to Constraint-Induced Aphasia therapy using both EEG and fMRI methods. This research will be carried out in collaboration with Bettina Mohr at Anglia Polytechnic University and Elizabeth Warburton and Jean-Claude Baron at the Stroke Unit of Addenbrooke's Hospital Cambridge (see SL4.5).

L4.5 Further research

In a long-lasting collaboration, Bettina Mohr and Friedemann Pulvermüller are investigating the effect of redundant stimulus information on the speed and accuracy of cognitive processes. The redundancy gain, the improvement of processing with redundant information, has been shown to be particularly strong for stimuli that have been learned (words, known faces, common objects), whereas it is reduced or absent for uncommon material for which no cortical representation can be assumed (pseudo-words, unknown faces, non-objects) (Mohr, Pulvermüller, & Zaidel, 1994). The redundancy gain to words was also found to be absent in patients with commissurotomy (Mohr, Pulvermüller, Rayman, & Zaidel, 1994), and recently, we observed that absence of the redundancy gain characterizes one other syndrome for which a dysfunction in interhemispheric interaction has been suggested, namely schizophrenia (Mohr, Heim, Pulvermüller, & Rockstroh, 2001; Mohr, Pulvermüller, Cohen, & Rockstroh, 2000). In a series of studies with healthy subjects, the influence of varying stimulus onset asynchronies on the redundant target effect for words was investigated. The redundancy gain vanished at minimal SOAs (50 ms), but an additional word-specific facilitation effect was found at an SOA of ~150 ms (Mohr & Pulvermüller, 2002). We interpret these results in terms of the activity dynamics of cortical representations.

In a collaboration with Christian Dobel at the Max Planck Institute of Psycholinguistics in Nijmegen, we looked at cortical laterality of neurophysiological processes while aphasics and normal control subjects performed syntactic and semantic tasks. A recent result was that there is strong right-lateralization of brain activity during the task aphasics have most problems with (the syntactic task in our study) whereas laterality of neurophysiological responses to the left lesioned hemisphere was seen during the task where performance was relatively intact (the semantic task) (Dobel et al., 2001). These results support theories of language recovery after stroke postulating that language-related activation of the right hemisphere is not an effective compensatory strategy (Heiss, Kessler, Thiel, Ghaemi, & Karbe, 1999). We have also looked at neurophysiological changes in normal subjects that can be induced by learning and lead to an alteration of word processing (Pulvermüller, Mohr, Schleichert & Veit, 2000).

The collaborations undertaken at the CBU with Robert Carlyon, where the neurophysiological correlates of the continuity illusion were investigated, and with William Marslen-Wilson, where Mismatch Negativity indicators of morphological processing have begun to be investigated, are specified in the project descriptions A3 and L2.2.5, respectively.

AWARDS AND HONOURS

Ingrid Johnsrude was elected to a Non-stipendiary Research Fellowship of Clare Hall College, Cambridge in October 2002. Friedemann Pulvermüller elected to membership of the Rodin Remediation Academy, Stockholm, 2002. William Marslen-Wilson has held a visiting Professorship in the Department of Psychology, Birkbeck College since July 1997, and was installed as a Fellow of the College in March 2000. He was the Wei Lun Visiting Professor at the Chinese University of Hong Kong in April 2000, and gave the annual Drever Lecture at the University of Edinburgh in April 2002. He was elected to an Honorary Professorship of Language and Cognition at the University of Cambridge in September 2002.

PUBLICATIONS

Refereed Journals

Assadollahi, R. & PULVERMÜLLER, F. (2001). Neuromagnetic evidence for early access to cognitive representations. Neuroreport, 12, 207-213.

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B. Rockstroh & F. Pulvermüller (PIs) CI Aphasia Therapy, 2001--2002. StiftungZNS. ca. 50,000 €

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5. MEMORY AND KNOWLEDGE: DMS SECTION PROGRESS REPORT

Overview

The central goal of the Dementia, Memory and Semantics (DMS) programme of the CBU's Memory & Knowledge Group is to analyse the functional and neuroanatomical structure of long-term memory and language from evidence about disorders of these cognitive abilities, especially in patients with neurodegenerative disease. Additional sources of evidence in our multi-approach research programme include studies of normally functioning individuals (both behavioural and neuroimaging experiments); neuropsychological studies of individuals with static rather than progressive brain lesions; and the development of computational, connectionist models of cognitive function. The group is perhaps best known for effectively combining detailed neuropsychological assessments with neuroanatomical investigations on the one hand, and connectionist modelling on the other. Examples of these two combinations that have resulted in high-profile and influential work over the last decade include articles on the neuropsychology and neuroanatomy of semantic dementia (Hodges, Patterson, Oxbury & Funnell, 1992), on temporal patterns of impaired retrograde memory in Alzheimer's disease vs. semantic dementia (Graham & Hodges, 1997), and articles on connectionist models of reading and its disorders (Plaut, McClelland, Seidenberg & Patterson, 1996) and of the relationship between comprehension and naming (Lambon Ralph, McClelland, Patterson, Galton & Hodges, 2001). Our connectionist enterprise derives from Karalyn Patterson's long-term collaboration with the well-known modelling group in the USA led by Jay McClelland, Mark Seidenberg and David Plaut and supported by joint NIMH programme grants, with the third successive 5-year funding period starting in 2002. The facts that our neuropsychological studies are exceptionally well grounded in neurological/ radiological assessments, and that we are able to study whole case-series of patients with disorders especially germane to important theoretical issues, are attributable to John Hodges' position as Professor of Behavioural Neurology and to his MRC-funded programme of clinical research in the Cambridge University Department of Neurology. When the CBU's new programme of research under the directorship of William Marslen-Wilson was established in 1997, the DMS programme based jointly at the CBU and in Neurology was singled out by the MRC as critical to the future goals of the CBU and its role in a broader Cambridge-wide initiative in neuroscience.

We wish to emphasise three sine qua non for the success of the DMS programme that derive from its joint CBU/Neurology base. First, our main patient populations are those with neurodegenerative diseases – Alzheimer's disease, frontotemporal dementia, corticobasal degeneration, etc. Unlike patients with static lesions from cerebrovascular accident or tumour resection etc., who often improve or at least remain stable post-insult and are not necessarily 'ill', our patients steadily deteriorate. They require substantial and regular medical care, and their families require clinical attention and counselling, all of which is provided by the services associated with the clinics organised by John Hodges (the weekly Memory and Cognitive Disorders Clinic and the twice-monthly Early Dementia Clinic). The second vital aspect of this coordination is the extent to which our research benefits from the extensive clinical work-up that the patients receive. This benefit comes in the form of both clinical neuropsychological tests and neuroradiological investigations – typically structural MRI which, for neurodegenerative cases, needs to be repeated longitudinally. The third advantage provided by the symbiosis of the two programmes comes at the level of inter-disciplinary development: our approach fosters appreciation of theoretical work by clinicians, and of clinical methods by academic researchers. The benefits gained by the students and postdoctoral scientists who work in this cross-disciplinary environment endure well beyond the period of time that these individuals spend in our laboratory and percolate out into the research field in general.

As reviewed below, the central goal of DMS project M1 has been to advance our understanding of the internal organisation and neural basis of semantic memory, from studies of patients with semantic dementia (SD) and Alzheimer's disease (AD), functional imaging investigations of normal participants performing semantic tasks, and the intact and 'lesioned' behaviour of a new connectionist model of semantic memory developed by Timothy Rogers. Project M2 has addressed the relationships amongst forms of long-term memory (semantic, episodic, autobiographical) that are, at least in some theories, distinctly different. The primary approaches have been neuropsychological studies of retrograde memory in patients with SD, frontal dementia or AD; a novel functional imaging study of autobiographical memory in normal participants; and also an extensive programme of work on anterograde memory (new learning) in various patient populations. Project M3 consists of the DMS research on language. We have attempted to account for patterns of impairment in SD and AD on language tasks, such as those that tax receptive and expressive vocabulary, which are necessarily affected by semantic impairment. Another major component has addressed the performance of semantically or phonologically impaired patients on language tasks, such as reading aloud or inflecting verbs, for which our interactive models of language make specific predictions.

M1: The organisation and neural basis of semantic memory and knowledge

Scientific Direction: Hodges (45%), Patterson (35%), K. Graham (20%)

MRC-supported scientists: Kellenbach (100%), T. Rogers (60%), Bak (30%), Lee (20%) Grant-supported: Lambon Ralph (50%) Research support: Drake (34%), Erzinclioglu (33%), Wilkinson (33%)

Grant-funded research support: Everitt (100%), Donald (100%), Hearn (100%) MRC-supported students: Bozeat (100%), (50%), Simons (10%)

Grant-supported students: Clague (50%)

Background

"'Fodor's First Law of the Nonexistence of Cognitive Science': the more global a cognitive process is, the less anybody understands it" (Fodor, 1983, p.107).

What could be more global in human cognition than semantic memory, encompassing – as it is meant to do – our knowledge of all aspects of the physical and mental world plus the words that we use to talk about it? By Fodor's law, then, no-one should understand semantic memory. In fact, when he offered this assessment 20 years ago, it was probably appropriately pessimistic; but we believe that a more optimistic assessment would be appropriate today, and that this achievement is in large part attributable to the kinds of neuropsychological and modelling approaches that have characterised our work on semantic memory over the last quinquennium.

Because so much of this project has relied on studies of SD and/or AD, we begin with a brief account of these disorders. SD is now recognised as forming part of the spectrum of diseases referred to as frontotemporal dementia (FTD), a neurodegenerative disease associated with non-Alzheimer pathology at post-mortem. The syndrome of SD results from profound bilateral, asymmetrical atrophy of the anterior temporal lobe, more often with greater neuronal loss on the left side (L>R) but sometimes with more severe right-sided abnormality (R>L). Although semantic deficits occur in disorders other than SD (e.g. AD, herpes simplex virus encephalitis, following traumatic brain injury, etc.), the relative purity of the semantic breakdown in SD makes it ideal for studying (a) the cognitive architecture of semantic knowledge, (b) the impact of this dissolution on other cognitive processes, and (c) the neural basis of semantic knowledge. Our early papers on SD have become widely cited classics of the neuropsychological literature and have helped to promote world-wide interest in this syndrome. In addition to our more specific, theoretically governed research on this syndrome over the last quinquennium which is reviewed below, we have published a number of review papers and chapters with the goal of continuing to inform both neurological and cognitive communities about the nature and implications this disorder (e.g. Garrard & Hodges, 1999, 2000; Hodges, in press; Hodges & Miller, 2001a, b; Patterson & Hodges, 2000, 2001).

Our neuropsychological studies of semantic memory also involve patients with AD. In contrast to SD, the predominant cognitive deficit in AD is impairment of episodic memory, reflecting the fact that the medial temporal lobe (MTL) carries the brunt of pathology. Impaired performance on semantic tests such as category fluency and concept definitions are, however, also well-recognised features of AD. Some of our earlier studies (e.g. Hodges and Patterson, 1995; Hodges, Patterson, Graham & Dawson, 1996; Lambon Ralph, Patterson & Hodges, 1997) were influential in promoting the prevailing (though still not unanimous) view that these deficits in AD reflect genuine disruption to, rather than impaired retrieval from, semantic memory. We have also contributed to the characterisation of several now well recognised atypical presentations of AD (Galton, Patterson, Xuereb & Hodges, 2000).

M1.1 How many semantic systems?

M1.1.1 Objects vs. words

Our working hypothesis has been that when semantic knowledge about a concept (such as a zebra or a potato peeler) is activated in response to seeing a real exemplar of the concept, or by hearing or reading the concept's name, or by the intention to speak its name or to describe the object, it is the same distributed network of information that is activated. There will, of course, be important principled differences in the full activation patterns under these different conditions, resulting from links between semantic representations and brain regions more critically involved in processing words vs. objects as stimuli, and of processes needed to activate speech vs. action as responses. But with regard to central conceptual knowledge, we think in terms of a single distributed network. Therefore, although patients with central semantic deficits are most prominently impaired in producing and comprehending words, we predicted that they would also demonstrate abnormal performance on appropriate semantic assessments with pictures or real objects as stimulus materials and with non-verbal actions as responses. This theoretical position contrasts with a hypothesis of separate word-, object- and action-based semantic systems that can be independently damaged (e.g. Papagno & Capitani, 2001).

Our studies of semantic memory have involved the use of a battery of tests designed in the early 1990s and then updated about five years later (in collaboration with Dr Peter Garrard, an MRC Training Fellow at Addenbrooke's Hospital working with our group from 1996-1999). The battery assesses the status of conceptual knowledge about the same set of concrete-concept target items across a range of tasks differing in the modality of input and output. In support of the hypothesis of a modality-general semantic network, patients with SD showed striking parallels in concept definitions produced in response to pictures of these objects and (on a separate occasion) to the corresponding object names (Lambon Ralph, Graham, Patterson & Hodges, 1999b). As always in this disorder, success was strongly modulated by stimulus frequency or familiarity; but there were no cases even approaching a classical dissociation with respect to stimulus modality in either direction. Most patients' performance was mildly better in the picture condition, a difference that we attribute to the relationship between stimulus surface form and meaning which is wholly arbitrary in the case of words but partially systematic for objects or pictures. This difference is well captured by our connectionist models of conceptual knowledge (Rogers et al., submitted-a). The only two patients who produced more information in response to words than pictures both had R>L atrophy, and we attribute their pattern to disruption of visual/structural processing that seems to depend critically on right-hemisphere temporal lobe structures (Kellenbach, Hovius & Patterson, submitted).

The view that there is a specialised (and more robust) semantic system relating to objects and actions still enjoys wide support (e.g. Lauro-Grotto, Piccini & Shallice, 1997). We have tackled the issue in our research with SD patients in several additional ways. To begin with, we designed a series of entirely non-verbal semantic tasks involving (a) the matching of different pictures on the basis of conceptual knowledge, (b) the matching of pictures of objects to their characteristic sounds, and (c) delayed copying of drawings of familiar objects (Bozeat et al., in press-a; Bozeat, Lambon Ralph, Patterson, Garrard & Hodges, 2000). These experiments demonstrate not only consistent deficits in SD on all of these non-verbal tasks but also, as predicted by our hypothesis, extremely high correlations between degree of deficit on verbal and non-verbal semantic tasks. Results from the copying tasks are particularly striking. SD patients have normal ability to copy a line drawing of a familiar object that is in front of them; but when asked to study a drawing and to reproduce it after a brief filled delay, their responses both simplify and complicate the target drawing in ways that fit our understanding of the nature of the deficit. That is, after imposition of a short delay, the patients' drawings become much more prototypical: camels lose their humps and ducks acquire four legs. This suggests a broadened 'basin of attraction' for frequent and typical exemplars of a category, which can be observed in the verbal domain when the patients name camels and ducks as "dog" or "animal" and in the non-verbal domain when they draw camels and ducks that look like dogs.

M1.1.2 Do actions speak louder (or more successfully) than words?

In view of persistent claims in the literature that "action semantics" can be selectively preserved when other conceptual knowledge is compromised, we have explored the ability of patients with SD to use everyday objects (such as pencil sharpeners, match boxes, potato peelers and screwdrivers). A series of experiments designed to evaluate the ability of SD patients to use real exemplars of these objects, in relation to the patients' naming of and other kinds of knowledge about the exact same items, has demonstrated (a) that the patients invariably have (familiarity-modulated) deficits in real object usage which reflect degraded knowledge rather than impairment in praxic abilities or mechanical problem solving skills, the latter two being strikingly well preserved in SD (Hodges, Bozeat, Lambon Ralph, Patterson & Spatt, 2000; Hodges, Spatt & Patterson, 1999); (b) that degree of success/failure in object usage can be strongly predicted by performance on naming and semantic matching tests for the same items (Bozeat, Lambon Ralph, Patterson & Hodges, in press-b); (c) that aspects of action which are systematically related to object affordances, although restricted in scope, are relatively preserved under semantic impairment (Bozeat et al., in press-b); and (d) that – as originally demonstrated by Snowden, Griffiths & Neary (1994) – the patients are markedly more successful at using specific exemplars of common objects with which they have personal and recent experience than equally good exemplars provided by the experimenter (Bozeat, Lambon Ralph, Patterson & Hodges, 2002). The precise interpretation of this latter effect is debated, but our interpretation is that it reflects relatively preserved stimulus-specific procedural and episodic memory in SD rather than genuine enhancement of conceptual knowledge by everyday experience. The opposite pattern to that seen in SD – i.e. severely impaired object use due to disrupted praxis and mechanical problem-solving ability, despite preserved knowledge of how objects are meant to be used – occurs in patients with corticobasal degeneration, a degenerative disorder involving basal ganglia, frontal and parietal cortices (Spatt, Bak, Bozeat, Patterson & Hodges, 2002).

M1.1.3 Object recognition

A related topic of debate in the cognitive neuropsychological literature has been the extent to which conceptual knowledge is necessary to recognise an object as familiar, i.e. something that has been encountered before. Some theorists (e.g. Humphreys, Riddoch & Quinlan, 1988) have argued in favour of a pre-semantic structural description system that can function normally to identify a visual stimulus as a familiar object even if the semantic system itself is degraded, whereas our more interactive view of object processing predicts impaired recognition under these conditions. Consider the object decision tests, which have become standard for assessing this issue, in which participants are asked to judge whether pictures represent real or non-real objects. We predicted and have now confirmed that object-decision success by SD patients depends crucially on the relative plausibility/ typicality of the real and non-real objects in the stimulus set (Hovius, Kellenbach, Graham, Hodges & Patterson, in press; Rogers, Lambon Ralph, Hodges & Patterson, submitted-b). Particularly dramatic were the results from the latter study in which the patients were asked to make two-alternative forced-choice object decisions in two conditions: one where the more typical visual form for an animal (e.g. having a tail, not having a hump) applied to the real item in the pair (e.g. a lion with/without a tail; a donkey without/ with a hump), and the other where typicality was higher for the non-real animal (a gorilla without/with a tail; a camel with/without a hump). The SD patients achieved excellent performance in the former condition but were significantly impaired (to varying degrees across patients, which correlated with severity of semantic deficit) in the second condition. These results support our hypothesis that, even if there is a pre-semantic structural description system, its interaction with semantic representations is essential to its normal function.

In a recent PET study (Kellenbach et al., submitted), normal subjects revealed significantly increased activation of left temporal-lobe regions when making decisions (to pictures of objects) requiring knowledge of object colour or encyclopaedic facts; but the posterior inferior temporal area (Brodmann Area (BA) 37) in the right hemisphere was the principal locus for differential activation in an object-decision condition. On the reasonable assumption that there are strong neural connections feeding back from more anterior areas to posterior regions of both temporal lobes (Gloor, 1997), we interpret the object-decision findings in SD as reflecting impaired communication between severely atrophied anterior regions and structurally largely-unaffected posterior regions that cannot now function normally owing to this reduced input. This fits with results from our functional activation PET study with SD patients (Mummery, Patterson, Wise, Vandenberghe, Price & Hodges, 1999): associative semantic decisions about words and objects, which probably rely principally on anterior temporal areas, also activated posterior left BA 37 in normal subjects but not in four SD patients.

M1.2 Categorical and / or hierarchical organisation of semantic memory?

M1.2.1 Semantic categories

One of the most intriguing and controversial findings in cognitive neuroscience has been that neurological patients may have disproportionately disrupted knowledge of particular semantic or linguistic categories. The best documented double dissociation is between living things (or natural kinds) vs. manmade items (or artefacts). Our own studies of AD patients have revealed a small, but consistent, advantage for naming of artefacts over natural kinds in the majority of cases (Garrard et al., 2001b). The discrepancy increases with disease severity and does not seem attributable to stimulus variables (word frequency, age of acquisition etc.), or to inherent difficulty since a few patients showed the opposite pattern. To explain these findings we have argued that the pathology in the majority of AD cases spreads out from the hippocampal formation into infero-lateral temporal neocortex, thus causing disproportionate disturbance of visually-based knowledge which may be critical for the more subtle differentiations required to identify natural kinds. By contrast, the rare AD cases with poorer performance on artefacts have had unusually severe parietal lobe involvement (Garrard, Patterson, Watson & Hodges, 1998; Garrard et al., 2001b). Many patients with SD also display a small advantage for artefacts over natural kinds (Garrard, Lambon Ralph & Hodges, 2002). The reason why so few SD cases are characterised by a major disadvantage for natural kinds remains mysterious, especially in light of the robust deficit for knowledge of sensory/perceptual aspects of conceptual knowledge in SD (Lambon Ralph et al., 1999b; Lambon Ralph, Patterson, Garrard & Hodges, submitted). In agreement with Tyler et al. (in press), our PET investigations of this issue in normal participants have failed to uncover significant or consistent activation differences associated with natural vs. artefact domains, and instead have revealed differential activations associated with feature type (perceptual vs. non-perceptual aspects of conceptual knowledge: Lee et al., 2002a; Mummery, Patterson, Hodges, Wise & Price, 1998).

M1.2.2 Linguistic categories

A second dissociation of long-standing interest in neuropsychology is between objects/nouns and actions/verbs. Modelled on the widely used Pyramids and Palm Trees test of associative semantic knowledge about objects (in which the subject must decide that the palm tree rather than the pine tree "goes with" an Egyptian pyramid), we designed a test of associative semantics for actions/verbs, called the Kissing and Dancing test. The most striking finding from joint administration of these two assessments has been disproportionately poor Kissing-and-Dancing performance in patients with motor neurone disease (MND) with dementia (Bak, O'Donovan, Xuereb, Boniface & Hodges, 2001b), and also in patients with the frontal variant of FTD (Bak & Hodges, in press). Post-mortem brain examination in a subset of the MND cases has shown severe neuronal loss in the inferior frontal lobe (BA 44/45), in keeping with the hypothesis that action/verb knowledge is associated with frontal cortical and/or basal ganglia regions (Bak & Hodges, 2001; Pulvermuller, Haerle & Hummel, 2000). It is not yet clear whether this dissociation is single or double: although some SD patients achieve better scores for actions than objects, the difference is less dramatic/consistent than the reverse contrast associated with frontal abnormalities. Furthermore, a different approach to the noun/verb question in SD attributed the slightly greater preservation of verbs than nouns in their impoverished spontaneous speech to the impact of stimulus/response frequency on all aspects of SD impairments (Bird, Lambon Ralph, Patterson & Hodges, 2000).

M1.2.3 "I never forget a face"

A third domain of potential categorical organisation relates to knowledge about people vs. objects. In collaboration with Dr Siân Thompson (MRC Training Fellow at Addenbrooke's Hospital, 2000-2003), we have devised a famous-person naming test of graded difficulty (parallel to Warrington's graded difficulty object naming test) and a new battery assessing semantic knowledge of famous people (modelled on our general object/animal battery). With these improved assessments, we have recently replicated (Thompson et al., submitted) earlier observations of an SD patient with R>L temporal atrophy and severe loss of knowledge about famous people in the absence of significant impairment on our general semantic battery (Evans, Heggs, Antoun & Hodges, 1995). The interpretation of this result with regard to right-temporal specialisation for knowledge of people is, however, complicated by the fact that patients with mainly left-sided pathology typically also perform poorly on person-based tests of knowledge (Hodges & Graham, 1998). A significant disruption to knowledge about famous people, which manifests mainly as difficulty in naming them, is also an early and consistent finding in patients with AD (Hodges & Greene, 1998). It remains to be determined whether the vulnerability of this knowledge is primarily another manifestation of the fact that more specific aspects of conceptual knowledge suffer first in progressive degradation of semantic memory. People are unique individuals, whereas knowledge of objects or animals relies on accumulated experience with many exemplars of the concept.

M1.2.4 Modelling

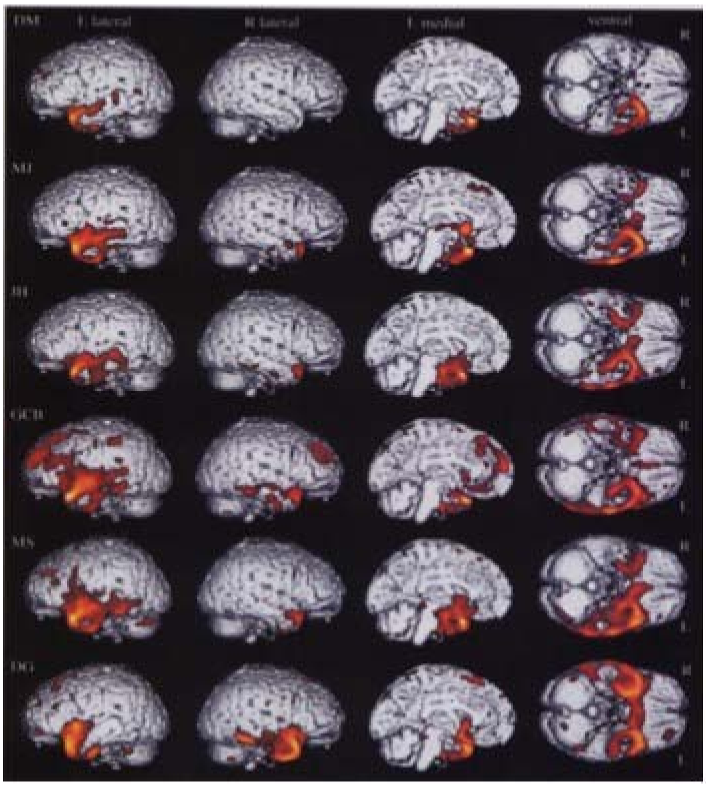
Apart from documenting the marked effects of specificity and prototypicality in patients with semantic deterioration, our investigations of these factors have centred on connectionist models in which these principles are inherent to the nature of representations. In a distributed semantic space, properties common to many semantically related items (such as four legs, two eyes and a tail for animals) benefit from mutually supportive connection weights. Atypical properties – those that serve to differentiate a given concept from its close semantic neighbours (e.g. penguins cannot fly; gorillas have no tail; zebras look very much like horses but happen to have stripes) – enjoy no such benefit and, under semantic degradation, suffer disproportionately. Thus, as already mentioned, patients with SD tend (a) to choose the gorilla with a tail (even though they can never have seen such a thing in real life) in a forced-choice object decision test; (b) to copy realistic line drawings of animals after a short delay by putting four legs on birds or snakes; (c) to name objects by assigning labels of the general category (zebra → "animal") or of more prototypical category coordinates (zebra → "horse"; one SD patient, after confidently responding "horse" to a picture of a zebra, pointed to the stripes and asked "but what are these funny things for?"); (d) to sort objects or words more successfully on the basis of general than specific distinctions; and so on. All of these features emerge spontaneously in a connectionist model of semantic memory (Rogers et al., submitted-a) which learns to translate between different surface representations such that it can simulate standard neuropsychological tasks such as object naming (visual representation → name), drawing to dictation (name → visual representation), concept definitions (picture or name → verbal attributes), naming to description (verbal attributes → name), etc. Whereas models of semantic memory – connectionist or otherwise – have typically assumed that semantic representations consist of feature lists, a key aspect of this model is that the semantic representations have no explicit content: they are, in effect, the hidden unit representations that arise from learning about relationships between the content-bearing surface representations associated with stimuli and responses. Thus the attributes that people can list for concepts (e.g. "a zebra is a horse-like large African herbivore with black and white stripes") are not viewed as constituting or directly reflecting the explicit contents of semantic representations. These are instead features that the model learns to comprehend as input or to produce as output when it needs to translate between different surface forms.

One reason that we consider this to be a valuable way of construing semantic memory is that one no longer needs to confront the difficult question of whether there are separate semantic systems associated with different modalities or feature types. In this conception, the answer is both yes and no. The visual and verbal representations that enable processing of stimuli and generation of responses are separate (though interacting) sources of information; but they are not central semantic sub-systems. This fits well with recent functional imaging studies of normal subjects, in which we have demonstrated significantly different selective regions of activation associated with different components of object knowledge – e.g. the typical sizes, colours, sounds or actions associated with familiar objects. As predicted more than a decade ago (Allport, 1985), these selective activations are often in or near brain regions involved in sensory or motor experience with the attribute type. Thus colour and size judgements activated visual areas in the posterior inferior temporal lobe, while sound judgements activated the superior temporal gyrus, an auditory region (Kellenbach, Brett & Patterson, 2001); and responses to manipulable (in conrast to non-manipulable) objects activated a region of ventral pre-motor cortex (Kellenbach, Brett & Patterson, in press). We interpret these activations as reflecting the content-bearing representations associated with stimuli and responses. These representations are then linked by the abstract semantic representations that must learn how to put all of this content together such that each modality- or attribute-specific region can talk to the others.

M1.3 The neuroanatomical basis of impaired semantic memory as assessed by structural imaging

In our initial studies of SD, we observed consistent asymmetrical atrophy of the anterior temporal lobe, and suggested a key role for this region bilaterally in semantic processing. More recently, the results of convergent structural imaging methods have confirmed and refined this early observation. Our first quantitative study used voxel-based morphometry (VBM) to measure the extent of reduction of grey matter in specific cortical regions in six patients with SD (Mummery et al., 2000). All six cases had significant atrophy in the anterior infero-lateral temporal lobe on the left, though one revealed even more profound atrophy in the same region on the right (see Figure 1). One very early case, in whom abnormalities were as yet only measurable on the left side, also showed abnormal semantic performance only on the most challenging tests, which is consonant with an assumption of bilateral representation of conceptual knowledge.

Figure 1. Regions of significantly reduced grey matter density in each of six SD patients relative to a group of age-matched normals. From left to right: the left lateral surface, right lateral surface, left medial surface and ventral surface of the brain are depicted on a three-dimensional rendering of a standard MRI scan. The figures are thresholded at $p < 0.001$ (uncorrected) to show the extent of damage.



The results of a larger SD group study (n=18), using a volumetric method of tracing defined cortical regions on coronal MRI (in ANALYZE), again confirmed consistent and severe atrophy involving the temporal polar cortex and the fusiform, parahippocampal and inferior temporal gyri (Galton et al., 2001b). The degree of semantic impairment on a variety of measures (category fluency, naming, Pyramids and Palm Trees semantic association) correlated most highly with the volume of the left fusiform gyrus: the latter consists mainly of Brodmann Area 20 but with contributions from BA 35/36, the perirhinal cortex. In addition, the measures of expressive vocabulary (naming and category fluency) correlated significantly with degree of atrophy in other left temporal regions including temporal pole and inferior and middle temporal gyri. One unexpected finding was significant asymmetric hippocampal atrophy in SD which, on the left, was equivalent to or greater than that in the AD cases included in this study (see Chan et al., 2001 for a similar finding). Although this degree of left-sided hippocampal abnormality in SD was not predicted, it does fit some of our behavioural and cognitive findings. For example, whereas recognition memory for pictures of objects can be normal in SD (see Progress Report for M2), episodic memory/learning for verbal material (especially as measured by recall but even by recognition) is very impaired (K.S. Graham, Patterson, Powis, Drake & Hodges, 2002).

M1.4 Summary

Our findings in this domain over the last five years, from all of the main approaches employed (neuropsychology, structural/functional imaging and connectionist modelling), suggest that semantic memory is both one and many systems. Different modalities of input to/output from conceptual knowledge, and different aspects of such knowledge, place particular demands on processing that recruit partially specialised brain regions; but the core of semantic memory, which enables people to translate between different modalities and coordinate different aspects of knowledge so as to behave in the real world, is a single distributed system. Neurological damage to this system, associated mainly with bilateral anterior temporal atrophy, disrupts all coherent behaviour, including use of familiar objects that has often been considered a separate module. Aspects of knowledge that are shared amongst many related concepts are robust; aspects that are unusual deteriorate rapidly under semantic degradation, yielding a system that responds mainly to typicality.

Project M2: The behavioural and neural relationship of semantic memory to episodic and autobiographical memory

Scientific Direction: K. Graham (70%), Hodges (45%), Patterson (15%)

MRC-supported scientists: Lee (80%), Bak (40%) Research support: Erzinclioglu (34%), Drake (33%), Wilkinson (33%) Grant-funded research support: Powis (100%) MRC-supported students: Kropelnicki (100%), Simons (90%) Grant supported students: A.Graham, Clague (50%)

M2 is concerned with the organisation and neural basis of long-term memory, in particular the influential distinction, first proposed by Tulving (1972), between episodic and semantic memory. Episodic memory refers to personally experienced and temporally specific events, the retrieval of which is said to be associated with "autonoetic" conscious awareness (or "mental time travel", Tulving, 2001). Semantic memory, as discussed in detail in M1, refers to our store of representational knowledge including facts, concepts, and the meaning of words. Tulving initially proposed that episodic and semantic memory were cognitively and neurally separate systems, based on findings from patients such as the famous HM (Scoville & Milner, 1957), who suffered severe episodic memory deficits after surgical removal of structures in the MTL, but showed little evidence of semantic memory impairment. This led researchers to conclude that the neural basis of episodic memory was the MTL, and that damage to this region would result in a selective loss of episodic, but not semantic memory. Further studies in amnesia, however, challenged this view, and led to the development of more sophisticated models of long-term memory.

M2.1 Memory consolidation

One of the first problems with a simple fractionation between episodic and semantic memory was the fact that the episodic memory impairment seen in amnesia was often not complete. Some patients were able to retrieve memories from the remote past (e.g. childhood or early adulthood) despite their inability to recall recent events (Rempel-Clower, Zola, Squire & Amaral, 1996). This result implies a process of memory consolidation in humans, whereby new memories are initially dependent upon MTL regions, especially the hippocampus, but become consolidated over time in other brain regions (e.g. temporal neocortex). This account of how human long-term memories are acquired and stored has been termed the standard model (Squire, 1992), and a major focus of our research over the last five years has been the applicability of this model to profiles of remote memory, predominantly in patients with dementia.

M2.1.1 Reverse temporal 'gradient' in SD

Until our recent work, the majority of research on memory consolidation had focused on patterns of remote memory in patients with nonprogressive damage to MTL regions, in particular asking whether such patients show a temporal gradient (recent < remote) in recall of semantic and autobiographical information. Our goal, however, has been to investigate the opposite, and previously unspecified, hypothesis that temporal neocortical damage would be more likely to impair recall of remote compared to recent memories. Patients with SD provide a unique opportunity to investigate this prediction, as they present with focal atrophy to temporal neocortical regions, with asymmetrical involvement of medial temporal structures (see M1.3). Our first experiment on this topic reported a double dissociation in the recall of personal events from the past (so-called autobiographical memory). While cases with SD showed better retrieval of personal events from recent life compared to childhood and early adulthood, a matched group of AD patients were better at retrieving memories from the remote compared to recent past (K.S. Graham & Hodges, 1997). Further studies revealed that the reverse temporal gradient in SD extends to remote semantic memory, including tests of event knowledge (K.S. Graham, Pratt & Hodges, 1998) and recognition/identification of famous names (Hodges & Graham, 1998). In addition, these investigations confirmed that patients with SD actually show a more step-like profile, as opposed to a gradient, in performance, with better recall of only very recent events from the last 2-3 years of their lives. These findings have received considerable attention from memory researchers around the world, and are strongly consistent with the standard model (Murre, Graham & Hodges, 2001).

M2.1.2 Multiple trace model

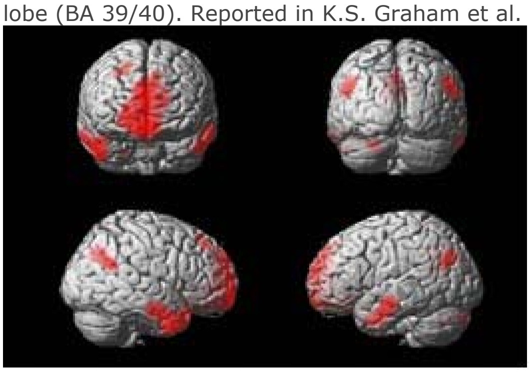
Notably, however, in the last few years the standard model has been contested. Nadel and Moscovitch (1997) noted that many patients with bilateral hippocampal damage show autobiographical memory deficits that are temporally extensive (Cipolotti et al., 2001); this pattern suggests that the hippocampus may play a more permanent role in the retrieval of all episodic memories regardless of their age. While this new memory consolidation model, termed the Multiple Trace Model (MTM), is relatively compelling, at least in terms of how it can account for the behavioural data from patients with focal MTL lesions, it has significant difficulty explaining the reverse step function documented in our patients with SD. In response to a commentary on this issue (K.S. Graham, 1999), Moscovitch and Nadel (1999) proposed a number of alternative explanations for the time-limited pattern in SD: (a) that there was only one reported patient showing this pattern on a sufficiently detailed autobiographical test; (b) that the profile may be due to strategic retrieval deficits caused by concomitant frontal pathology; and (c) that verbally-based testing of autobiographical memory may have exacerbated the degree of remote memory deficit. A series of investigations carried out in our Cambridge population have confirmed, however, the replicability of our initial finding across a variety of verbal and non verbal autobiographical tasks in both group and detailed single-case studies (K.S. Graham, Kropelnicki, Goldman & Hodges, in press; K.S. Graham, Lambon Ralph & Hodges, 1999a; K.S. Graham et al., 1998; Hodges & Graham, 2001; Nestor, Graham, Bozeat, Simons & Hodges, 2002). A further unpublished study by Anna Kropelnicki (MRC PhD student, 1999-2002) revealed that linguistic factors do not account for the time effect. These findings imply that remote autobiographical memories are truly inaccessible in patients with SD, and as discussed in detail in Nestor et al. (2002), lead one to question the exact role of the hippocampus in the MTM. For example, if the hippocampus acts as a pointer or indexer to the – presumably widely distributed – neocortical elements supporting the content of autobiographical events (as proposed by Moscovitch & Nadel, 1999), why can the hippocampus (which seems to be functionally preserved in SD, at least on the right) not activate components of remote episodic events dependent upon non-damaged neocortical regions (such as the occipital and parietal lobes, which may also be involved in autobiographical memory Maguire & Mummery, 1999; Rubin & Greenberg, 1998)?

M2.1.3 Relationship between autobiographical and semantic memory

One possible explanation consistent with the MTM is that the process of reconstructing autobiographical memories from the past is heavily dependent upon conceptual knowledge. Contrary to this hypothesis, however, is the case reported by Kitchener and Hodges (1999), who showed poor semantic memory, particularly for famous people but also for objects, yet performed well on tests of autobiographical memory. A further SD case study revealed no evidence that increasing the specificity of autobiographical cues improved accessibility to past personal events (K.S. Graham et al., in press), a result that is difficult to explain in terms of Moscovitch and Nadel's (1999) 'semantic' account.

To investigate the relationship between autobiographical and semantic memory in more detail, we carried out a series of neuroimaging studies of long-term memory at the Wolfson Brain Imaging Centre, Addenbrooke's Hospital. While autobiographical memory impairments in patients typically result from right-sided or bilateral temporal lobe lesions (Conway & Fthenaki, 2000; Kopelman & Kapur, 2001), neuroimaging investigations have highlighted a left-lateralised network of regions, including temporal pole, middle temporal gyrus, hippocampus, and medial prefrontal cortex (Maguire, 2001). There are, however, a number of problems with these latter investigations, such as the use of recognition, as opposed to recall, tasks (Maguire & Mummery, 1999) and insufficient length of time for autobiographical retrieval (Conway et al., 1999). To address these problems, our three PET studies employed tasks similar to those in our patient experiments (K.S. Graham & Hodges, 1997; Lee et al., 2002a; Nestor et al., 2002), which allowed us to test retrieval of semantic knowledge (of objects, animals and people) versus autobiographical memories in response to the same words. Consistent with the neuropsychological findings, we found clear evidence of bilateral anterior temporal lobe involvement in the retrieval of autobiographical memories (K.S. Graham, Lee, Brett & Patterson, submitted-b, see Figure 2).

Figure 2 Retrieval of autobiographical memories contrasted with recall of semantic facts revealed significant activations in the middle/inferior temporal gyri (BA 20), medial frontal cortex (BA 9/10) and inferior parietal lobe (BA 39/40). Reported in K.S. Graham et al. (submitted-b).



This finding implies that many neuroimaging experiments (Maguire & Mummery, 1999) have adopted – inadvertently – tasks that only require retrieval of autobiographical knowledge (e.g. I was on sabbatical at Berkeley), as opposed to a specific episodic event (e.g. I skied too fast round a corner at Lake Tahoe and ended up head first in a snow drift). Interestingly, the activations in the temporal lobe for autobiographical recall were virtually identical to those seen when recall of information about famous people (or famous events) was contrasted with retrieval of general semantic facts. This finding lends some support to the notion that recall of autobiographical memories may be dependent upon some aspects of semantic memory (as proposed by Moscovitch & Nadel, 1999), although it is important to note that while functional neuroimaging provides clues about the regions involved in a cognitive process, it cannot tell us which of these regions are critical for this behavioural task.

Our research on poor autobiographical memory in the context of normal semantic memory has included detailed studies of patient JM (Evans, Breen, Antoun & Hodges, 1996; Evans, Graham, Pratt & Hodges, in press), who suffered diffuse neocortical lesions after cerebral vasculistis, and of patients with the syndrome of transient epileptic amnesia (Manes, Zeman, Graham & Hodges, 2001). Patient JM is a good example of focal retrograde amnesia, with profound impairments in autobiographical memory in the context of normal anterograde and semantic memory. A follow-up study confirmed that she could acquire new autobiographical events despite her difficulties retrieving old memories from the past (Evans et al., in press). These studies reveal that at least two different processes can result in an isolated autobiographical memory deficit: (a) diffuse neocortical damage insufficient to cause loss of semantic memory but resulting in damage to cortico-cortical connectivity (as in JM), and (b) damage to strategic retrieval processes critical for autobiographical recall, as seen in some patients with frontal and thalamic lesions (Hodges & McCarthy, 1993), and in cases with frontal variant FTD (fvFTD, Nestor et al., 2002).

Further support for the last point has also come from recent re-analyses in patients with AD. Although many studies find evidence in support of a typical temporal gradient in AD (K.S. Graham & Hodges, 1997; Greene, Hodges & Baddeley, 1995), other experiments have failed to replicate this, even when using the same neuropsychological test (Nestor et al., 2002). A recent re-analysis of Greene and Hodges' AD data helped to resolve these discrepancies: while the majority of patients showed clear effects of time in autobiographical retrieval, a subgroup exhibited the flat profile predicted by Nadel and Moscovitch (1997). Strikingly, and contradictory to Nadel, Samsonovich, Ryan and Moscovitch (2000), there was no evidence that degree of remote memory impairment was related to performance on anterograde memory tests; in fact, the presence of an extensive and flat pattern was predicted by scores on tests of executive function (K.S. Graham, Goldman, Kropelnicki, Greene & Hodges, submitted-a). This intriguing finding suggests that the presence of extensive retrograde memory impairments in some non-progressive cases could, as in AD, be attributable to a frontally-based executive impairment.

M2.1.4 Role of the hippocampus in SD

As described in M1 above, our recent volumetric measurements of temporal lobe structures revealed that the degree of involvement of the left hippocampus in SD was largely indistinguishable from that seen in AD, although the SD patients had less MTL atrophy on the right side (Galton et al., 2001b). These findings initially seem problematic for the view that the relatively better recall of recent events in SD, and the poor memory in AD, is attributable to degree of atrophy in the hippocampi, and other MTL structures. Current cognitive and structural work, however, is aimed at investigating a number of possible explanations for these patterns, in particular whether these distinct profiles can be explained by the asymmetric nature of the pathology in SD. Structural work, carried out as part of John Hodges' clinical programme at Addenbrooke's Hospital, also indicates that differential involvement of anterior and posterior regions may be critical: Davies, Xuereb & Hodges (2002) found anterior hippocampal and entorhinal atrophy in SD with posterior involvement of these structures in AD. Parallel FDG-PET scanning has shown profound pan-limbic hypometabolism from a very early stage in AD (Nestor, Fryer, Smielewski & Hodges, submitted), while in SD the unilateral left-sided atrophy does not appear to affect the remainder of the limbic system (mammillary bodies, posterior cingulate, thalamic nuclei etc.).

M2.1.5 Cases with focal lesions to the MTL

While much of our research has focused on the patterns seen in SD and AD, we have also started addressing questions about memory consolidation, and the relationship between episodic and semantic memory, using cases with focal lesions to temporal lobe structures. Bak, Antoun, Balan & Hodges (2001a) reported two cases who suffered profound amnesia as a consequence of paraneoplastic limbic encephalitis, and noted that one patient showed no evidence of a remote memory impairment, despite significant difficulties on anterograde memory tasks. This type of pattern is not easily accommodated by the MTM, and further studies in patients with this rare condition are likely to be highly theoretically informative. In collaboration with Professor Narinder Kapur (Southampton University) we have also been investigating remote semantic memory in amnesia. Recent studies in cases with developmental amnesia (Vargha-Khadem, Gadian & Mishkin, 2001; Vargha-Khadem et al., 1997), reporting good learning of semantic knowledge despite profound episodic difficulties, concluded that there may be separate memory systems in the MTL, with the hippocampus and entorhinal cortex supporting the acquisition of context-dependent (episodic) and context-independent (semantic) memories, respectively. Kropelnicki, Graham, Kapur & Hodges (2002) tested this theory using a battery of tasks designed to investigate knowledge of vocabulary that had come into the English language at different time-periods over the past four decades. A group of adult amnesic patients, with bilateral MTL damage, demonstrated temporal gradients in their ability to define vocabulary, with a particular weakness in the decade (1970s) prior to their injury. In terms of vocabulary emerging after their neurological insult, there was evidence of good acquisition of gist (e.g. categorical) knowledge about the words, but the group performed less well than controls on a more difficult definitions task. There was no evidence that performance on memory tasks (especially recognition memory, a possible marker of non-hippocampal medial temporal damage) was related to vocabulary acquisition. These findings suggest that adult amnesics acquire new semantic knowledge via slow cortical learning, and has important implications for views about the role of MTL regions in new learning (see also M2.2).

M2.1.6 Summary

In conclusion, patients with SD and those with AD show distinct profiles in autobiographical and semantic memory retrieval: while most cases with AD show a standard temporal gradient (recent < remote), patients with SD typically recall more memories from the recent compared to the remote past. These patterns are problematic for the MTM, which does not predict such strong and replicable effects of time in these neurodegenerative diseases. Although Moscovitch and Nadel (1999) suggest that the pattern in SD, at least, might reflect the dependence of autobiographical retrieval upon semantic memory, some of our own neuropsychological studies are incompatible with this proposal (Graham et al., in press; Kitchener & Hodges, 1999). Our imaging study, however, did find remarkable overlap in the temporal lobe regions that were activated during retrieval of autobiographical memories and semantic knowledge of famous people and events, although it is not possible to know whether these regions are critical to these memory processes. While our data are most consistent with the standard model, it is clear that both views suffer from a serious lack of explanatory power: the standard model cannot account for patients who show extensive autobiographical deficits after bilateral hippocampal lesions, and the MTM is not able to explain profiles of remote memory in dementia. Further studies on this topic need to increase the specificity of the models, and to consider methods that will result in clearer predictions to be tested in neuropsychological populations.

M2.2 Is acquisition of new episodic memories dependent upon semantic memory?

Tulving (1995) has proposed that the registration of information in episodic memory is contingent upon access to and output from semantic memory, and writes, "a double dissociation between semantic and episodic memory is not possible and only single dissociations (impaired episodic memory and preserved semantic memory) can occur" (p.844). Over the last quinquennium, we have systematically investigated this topic in SD, and have demonstrated that episodic memory is not necessarily dependent upon normal functioning of the semantic system.

M2.2.1 Recognition memory for objects: a perceptual contribution

While our studies of autobiographical memory imply that cases with SD are able to acquire new memories, a number of other investigations have reported poor memory on standard measures of new learning, including recognition memory (Warrington, 1975). To address this controversy, our first study investigated recognition memory for pictures of real and non-real animals in patients with SD, AD and in control subjects (Graham, Becker & Hodges, 1997), and found a clear double dissociation. Our SD, but not AD, group showed similar levels of performance on this test compared to controls. In contrast, the SD patients were significantly impaired, compared to both control subjects and AD patients, on the study task in which they had to say whether the animals were real or not. Two further experiments have provided additional insights into the processes that support new learning in SD. K.S. Graham, Simons, Pratt, Patterson & Hodges (2000) found that a group of eight patients with SD showed normal recognition memory when the picture of the target item in the recognition memory task was identical to the item that had been seen at study. When the target item was changed between study and test (e.g. a round dial telephone was replaced with a push button telephone), however, the patients were significantly impaired (compared to control subjects) on items they were unable to name from a picture. This result suggests that loss of semantic knowledge only disrupts recognition memory when the target item is perceptually different from the studied item. This hypothesis was further supported by a case study assessing recognition memory for 'known' and previously familiar but now 'degraded' items. The only condition under which the patient showed poor recognition memory was perceptually different items for which the patient's conceptual knowledge was degraded. Recognition memory for all perceptually identical items and for 'known' perceptually different items was not significantly impaired.

M2.2.2 But what about faces?

This technique has since been extended to face recognition memory, in particular because previous studies in the literature suggested some vulnerability of this type of memory in SD (Hodges et al., 1992; Snowden, Neary

& Mann, 1996). An MRC PhD student Jon Simons (1997-2000) showed that (a) patients with selective left temporal lobe atrophy were not significantly impaired on the faces component of the Warrington Recognition Memory Test; (b) a group of patients with predominantly right temporal lobe atrophy performed poorly on the test; (c) within this group, the status of the parahippocampal gyrus (which includes the perirhinal cortex) was predictive of performance (based on a temporal lobe rating scale developed by Galton et al., 2001a); and (d) like the object data described above, face recognition memory was affected by a change of picture (e.g. photographs of the Queen with and without a head-scarf), but only for famous people who were no longer 'known' to the patients (Simons, Graham, Galton, Patterson & Hodges, 2001a, see Figure 3).

Figure 3: (a) Example stimuli from Simons et al. (2001a). (b) The performance, as measured by d prime, of DM (a patient with semantic dementia) on the perceptually identical (PI) and perceptually different (PD) conditions of a recognition memory task (contrasting 'known' vs. 'degraded' (labelled as 'unknown') stimuli.

This study indicates two interesting points about the neural organisation of recognition memory for faces: first, a particular dependence upon the right temporal lobe, and second, involvement of non-hippocampal medial temporal regions. A further study explored more directly the relationship between knowledge and recognition memory using a modification of the Pyramids and Palm Trees Test (PPT, Simons, Graham & Hodges, 2002), and attempted to replicate the neuroanatomical findings from the previous investigation. In a study phase, subjects made the usual PPT semantic relatedness judgement, then 10 minutes later they were presented with an item from the test phase (pyramid) and a new semantically related foil (sphinx) and asked to choose the one they had seen before. We again demonstrated a double dissociation in the performance of patients with SD and AD. Similar to Simons et al. (2001a), the recognition memory performance observed in SD, but not in AD, was largely explained by the extent of atrophy affecting the parahippocampal gyrus (including perirhinal cortex) bilaterally.

M2.2.3 Multiple inputs to MTL

The results of this series of experiments are illuminating with regard to current cognitive and neural models of long-term memory. First, they show that perceptual information will support new learning, typically in conjunction with, but even in the absence of, meaningful input from the semantic system. A wider implication of this view is that the medial temporal based episodic system receives multiple sensory inputs from many disparate areas of the brain only some of which are damaged in SD. Second, our data provide some evidence that parahippocampal regions (in particular, perirhinal cortex) may be critical for recognition memory (see Hodges & Graham, 2001), a view consistent with emerging theories from the animal literature that different MTL regions play distinct roles in memory (Aggleton & Pearce, 2001). A PET neuroimaging study with normal participants (Simons, Graham, Owen, Patterson & Hodges, 2001b) examined two related issues: (a) which neural substrates are involved in recognition memory for people and objects, and (b) whether recognition memory for perceptually-identical vs. perceptually-different stimuli would differentially activate perceptual and semantic regions. Although the experiment did not support the latter hypothesis, the study confirmed that recognition memory for people activated a bilateral anterior temporal network, while recognition of object stimuli was more left-lateralised and involved posterior temporal regions. Notably, these patterns of activation – despite being produced on a very different type of memory task – mirror almost exactly those documented in our series of PET experiments investigating autobiographical and semantic memory (K.S. Graham et al., submitted-b; Lee et al., 2002a; Lee, Robbins, Graham & Owen, 2002b), and provide further, independent, confirmation of findings from our neuropsychological studies.

M2.2.4 Expanding the multiple inputs view to words

In contrast to their good performance on different forms of non-verbal anterograde memory, patients with SD typically perform very poorly on classic clinical tests of verbal memory, such as story recall and recognition (Hodges et al., 1992). The experiments discussed above help us to understand this finding. If new learning in SD relies heavily upon intact perceptual processes, then one would expect performance on word-based tests to be particularly poor since words, unlike pictures and faces, have little in the way of perceptually rich or distinctive information; consequently, learning verbal stimuli is likely to be almost entirely dependent on semantic encoding. Furthermore, unlike pictures, there is an arbitrary relationship between the phonological (and orthographic) forms of the word and the associated semantic representation. Our multiple inputs view predicts, therefore, that experiments based on the learning of 'known' and 'degraded' words would produce an advantage for 'known' items but that, unlike pictorial stimuli, the amount of learning even for 'known' words may still be impaired compared to that seen in control subjects.

We evaluated this prediction using a well-known test of verbal learning, recall and recognition (Welsh, Butters, Hughes, Mohs & Heyman, 1991). A group of SD patients were first pre-tested on the entire Snodgrass and Vanderwart (1980) corpus of 260 pictures to determine sets of 'known' and 'degraded' words (based on naming and word-picture matching) matched for word frequency and length. In the subsequent list-learning experiment, patients with SD showed very poor immediate and delayed recall of both 'known' and 'degraded' words but with an advantage for 'known' stimuli. There was even a significant impairment of yes-no recognition memory, particularly for items that were no longer known to the patients. Analysis of the performance of individual cases showed a very marked effect of disease severity: despite the overall 'known' > 'degraded' advantage, patients with mild semantic breakdown showed good recognition memory for both classes of stimuli, and the most severely semantically-impaired patients were poor at recognition memory in both conditions (K.S. Graham et al., 2002). These findings are consistent with another study in a single case of SD, in which we investigated whether relearning of "forgotten" vocabulary was possible via repeated exposure to pictures of concepts and their written labels. DM showed a remarkable ability to improve his word production (as measured using category fluency), although any benefit was quickly lost when he ceased practicing, thereby limiting the long-term usefulness of this particular strategy (K.S. Graham, Patterson, Pratt & Hodges, 1999c). Notably, DM's practice only improved his word production abilities: there was no evidence that DM's learning generalised within semantic category (e.g. he rigidly produced only items he practiced). In a follow-up study, we confirmed that DM was often unable to retrieve semantic information about items he produced accurately in category fluency (K.S. Graham, Patterson, Pratt & Hodges, 2001). These three studies suggest that extensive exposure (or rehearsal) to verbal stimuli is necessary for patients with SD to re-acquire new vocabulary, and that this learning does not seem to extend to semantic knowledge about the concepts represented by the words. The findings are in agreement with collaborative work carried out by Linda Clare, Barbara Wilson and John Hodges, in which it has been demonstrated that errorless learning of associations (e.g. face-name) can be beneficial in early AD (Clare, Wilson, Breen & Hodges, 1999; Clare, Wilson, Carter, Breen, Gosses & Hodges, 2000; Clare, Wilson, Carter & Hodges, 2001, see M5). DM's anomia meant that he rarely produced errors during practice, and it is therefore possible that his improvement also benefited – inadvertently – from an errorless approach.

M2.2.5 Familiarity versus recollection

It has recently been proposed that two functionally separate processes contribute to recognition memory: "recollection" (episodic retrieval of the original learning episode) and "familiarity" (recognition of the prior occurrence of an event without associated contextual retrieval). While the experiments described above have demonstrated preserved recognition memory for pictorial stimuli in patients with SD, one possible explanation for this pattern is that patients may be performing these tests using judgements of familiarity rather than recollecting the study episode (Tulving, 2001). This possibility is important, as it may be that Tulving's model – in which semantic processing is a necessary contributor to episodic memory – only relates to recollective memory. Given our findings that patients with SD can retrieve recent autobiographical experiences (K.S. Graham & Hodges, 1997), which must require retrieval of some contextual aspects of the event (e.g. temporal and spatial information), it seems unlikely that the good pictorial recognition memory in SD is purely due to familiarity; but this topic has not, to date, been examined systematically.

We developed two novel experimental paradigms that allowed us to study the contributions of familiarity and recollection to performance on tests of episodic memory in SD (Simons et al., in press). SD patients (varying from mild to severe) and controls were asked to name two sets of 30 line drawings presented 5 minutes apart. After a 15 minute delay, memory for the pictures and their sources was examined by asking subjects to indicate whether the pictures were unfamiliar or belonged to Set 1 or Set 2. Seven of the 10 patients showed normal item detection, confirming that the ability to discriminate familiar from unfamiliar items is preserved in the majority of cases with SD, even on a demanding episodic memory task. The three patients who showed deficits were the three most semantically impoverished cases, although again there was no evidence from item-specific analyses that performance on individual items was influenced by knowledge of the concept depicted by the picture. In the source discrimination component, three out of ten patients showed impairment when asked to decide which set a picture belonged to, although these were not the most semantically impaired cases, indeed two were among the five mildest patients. These findings, and similar results from a visual-visual associative memory task, confirm that many patients with SD have both excellent familiarity and recollection of studied items, and that both these processes presumably contribute to the good recognition memory evident in the disease.

The neural basis of familiarity and recollection is controversial, but, at least for familiarity, there is some evidence from animal lesion studies that neurons in perirhinal cortex, but not in the hippocampus, respond to re-presentation of a stimulus. These findings have led researchers to propose that familiarity is dependent upon a perirhinal cortex/dorsomedial thalamic nucleus system, while recollection requires a hippocampal/anterior thalamic memory system (Aggleton & Brown, 1999). Our previous studies demonstrating correlation of recognition memory with measurements of non-hippocampal medial temporal regions concur with these findings. There was, however, no significant relationship between volumetric measures of hippocampal loss and performance on the source discrimination component of our memory test. Instead, the source discrimination scores achieved by the SD group were significantly correlated with degree of impairment on a battery of frontal executive tasks. This implies that the recollective decision in our source monitoring task (predominantly discrimination of temporal order) may not be hippocampally-mediated. To explore this relationship further, we studied a group of patients with the frontal variant of fvFTD and found, as predicted, marked impairment in source discrimination with good item detection (Simons et al., in press).

M2.2.6 Recollection of spatial context

An additional set of studies carried out in collaboration with Dr Barbara Sahakian (Cambridge University), based on the paired associated learning paradigm (PAL) in the CANTAB battery, has also been informative with respect to the question of recollection in patients with SD. This task requires subjects to learn the spatial location of increasing numbers of complex visual patterns (up to 8), a process that is thought to be dependent upon the hippocampus. A clinical project, investigating the usefulness of the PAL task in early diagnosis of dementia, has confirmed that the PAL is exquisitely sensitive to very early stage AD (Swainson et al., 2001). To investigate whether this test would differentiate between different dementias, and whether patients with FTD could perform a spatially-demanding recollective task, we gave this task to patients with SD and fvFTD. Both groups performed relatively well (especially patients with fvFTD), although some cases with SD were unable to complete the eight item problem (Lee, Rahman, Hodges, Sahakian & Graham, submitted). The results of this experiment suggest that recollection is not a uniform process dependent upon the hippocampus but instead reflects the nature of the material being processed: spatial information does recruit hippocampal structures while tasks that require temporal judgement are more likely to be critically dependent upon frontal processes. This hypothesis is being explored in more detail by Dr Andrew Graham, a Wellcome Training Fellow at the CBU (2001-2004).

M2.2.7 Summary

Our new learning experiments in patients with SD revealed that although semantic breakdown impairs anterograde verbal recall, other aspects of episodic memory, including recognition of (identical) pictures of objects and faces, source discrimination and even associative learning of visual and spatial information, can function independently of semantic memory. These findings are contrary to Tulving's (2001) view that the acquisition of episodic memory depends upon an intact semantic system. Instead, we have proposed that while episodic memory typically draws upon multiple inputs from perceptual and semantic systems, even when semantic knowledge is degraded perceptual information can be sufficient to support some forms of new learning (Simons et al., in press).

In terms of the opposite dissociation – good semantic memory in the context of poor episodic memory - our studies of vocabulary in adult amnesics are inconsistent with recent findings in developmental amnesia that the acquisition of episodic and semantic memory are dependent upon different MTL systems (see M2.1.5). Instead, we have argued that, while some semantic learning can occur in amnesia (via slow cortical learning), this will be qualitatively different from and less detailed than normal conceptual knowledge. At present, therefore, our findings are consistent with the idea that there is a single MTL system supporting the acquisition of both episodic and semantic memories, although we acknowledge that current cognitive tests of memory may not be sufficiently sensitive to discriminate the distinct functions of regions within the MTL.

Project M3: The role of semantic knowledge and other factors in language and its disorders

Scientific Direction: Patterson (50%), Hodges (10%), K. Graham (10%)

MRC-supported scientists: T.Rogers (40%), Bak (40%)

Grant-supported scientists: Bird (100%), Lambon Ralph (50%)

Research support: Wilkinson (34%), Erzinclioglu (33%), Drake (33%)

Grant-funded research support: Ellis (100%)

MRC-supported students: Bozeat (100%)

Grant-supported students: Knott (100%), Cumming (100%)

Much of this programme of research, consisting of neuropsychological studies and some modelling, is based on our working hypothesis that SD represents a relatively pure disintegration of conceptual knowledge, and that all observed cognitive deficits relate to this central underlying impairment. This predicts that aspects of language transparently dependent on semantic knowledge – particularly receptive and expressive vocabulary – must be compromised in SD, and the challenge is then to characterise these deficits in detailed and theoretically informed ways, to relate them to affected brain structures, to capture them in computational models, etc. But there is another sort of challenge: if our assumption is correct, then any documented deficits in aspects of language that are not so obviously dependent on semantic knowledge should also be interpretable in terms of the impact of a degraded semantic system. Language tasks under this description that have been a focus of attention in our work over the last quinquennium are reading aloud, spelling to dictation, verb inflection and verbal short-term memory. Our review begins with the more clearly semantic aspects of language, and then moves on to these other less expected linguistic bed-fellows of a deteriorating semantic system. The review also mentions those "other factors" in the project title: we are attempting to understand some non-semantic (mainly phonological) contributions to language disorders by studying Broca's aphasia in patients with lesions from cerebrovascular accident (CVA), and nonfluent progressive aphasia (the form of language disturbance in SD being fluent progressive aphasia; a description of the contrast between these two forms of progressive aphasia can be found in Patterson, Graham, Lambon Ralph & Hodges, in press).

M3.1 Naming and comprehension

Anomia is usually the most prominent presenting symptom of SD, and deficits in the comprehension of content-word vocabulary are rarely far behind. For example, when patients come to the neurology clinic, one of John Hodges's standard interview questions is "Do you have any hobbies?" Many SD patients, even at an early stage, reply "What's a hobby?". The deterioration of both expressive and receptive vocabulary is first and foremost a function of word frequency or familiarity (Lambon Ralph, Graham, Ellis & Hodges, 1998a). With regard to speech production, we demonstrated this effect by taking samples of narrative speech produced by normal individuals describing the "Cookie Theft" picture from the Boston Diagnostic Aphasia Examination (in which a boy in a kitchen is standing on a tipping stool trying to reach the cookies, and water from the sink is overflowing on to the floor). We then changed these samples by replacing all lower-frequency words with more common ones that would fit the context (e.g. stool was replaced by thing, overflowing by coming out, etc.). The distributions of word characteristics in these 'normal' narratives stripped of any lower-frequency nouns and verbs were good matches to the distributions of words in Cookie Theft narratives produced by SD patients, even on variables other than frequency (Bird et al., 2000).

Why are SD patients so profoundly anomic? The prevailing view in the literature on aphasia resulting from CVA is that naming difficulties can arise from several different underlying deficits: at a minimum, from disruption to knowledge of the concepts to be named (semantics), or to the representations of their names (phonology), or to communication between semantics and phonology (the semantics → phonology arrow). Disruption to phonological representations per se seems unlikely to be a major contributor to anomia in SD. Phonological errors (in which component phonemes of the target word are omitted or misplaced or exchanged, non-target phonemes are inserted, etc.) are common in most types of aphasia but very rare in SD naming or spontaneous speech; and the patients' virtually flawless repetition of single words likewise suggests uncorrupted phonological representations for speech production. In our earlier work, however, we did propose that anomia in SD could arise not only from semantic deterioration but additionally from insufficient activation of phonology by meaning. This was because we observed profound progressive anomia in a patient (FM) with only a mild and rather stable semantic deficit; indeed we labelled FM's pattern "progressive pure anomia" (K.S. Graham, Patterson & Hodges, 1995). Subsequent work, however, has led us to a somewhat different interpretation of these results.

All SD patients are anomic, but some are more anomic than others; and (with a nod towards George Orwell) it turns out that the 'less equal' ones in this instance are patients with greater atrophy on the left than the right (L>R). FM, whose atrophy had a strong left dominance, named 19% of a set of common objects at first presentation; a year later, when she was still functioning well in most aspects of cognitive testing and daily life, her naming had reduced to 6%. This suggested that the anomia in L>R cases reflected a deficit in semantics → phonology as well as in semantics itself.

A more satisfactory solution arose, however, from observations and hypotheses regarding the localisation of different aspects of language in the brain. Everything that we know about SD fits a hypothesis of bilateral temporal representation of semantics; but more than a century of research on aphasia suggests that speech production is left lateralised in virtually all right-handers and most left-handers. We therefore developed the hypothesis, and a corresponding computational model, in which semantic representations are bilaterally distributed, but phonological representations (a) are confined to the left hemisphere, and (b) receive much stronger inputs from their neighbouring semantic units on the left than from the more distant ones on the right (Lambon Ralph et al., 2001). As demonstrated in Figure 4, taken from that article, this model, when 'damaged' bilaterally but asymmetrically, produced an excellent fit to the relationship between naming and comprehension deficits in both R>L and L>R SD patients. FM's combination of naming and word-picture matching performance at one year post-presentation is almost perfectly captured by the point of sharpest inflection in the L>R simulation curve, with 88% correct word-picture matching but only 6% correct naming. In other words, even this extreme discrepancy between comprehension and naming scores can arise from a reduction in the neuron-like units comprising semantic representations, provided that these happen to be the semantic units most important for activating phonological representations

Figure 4. Comprehension vs. naming: direct comparison between grouped patient data and simulation results from a connectionist model. Patients: R>L = cases with more right than left temporal atrophy; L>R = cases with more left than right atrophy. Simulation: R>L = more right than left semantic unit damage; L>R = more left than right semantic unit damage.

M3.2 Two of the three R's: reading and riting

Our work on the impact of semantic degradation on 'non-semantic' language tasks began with a study of reading in SD patients, in whom we documented a consistent pattern of surface dyslexia (Patterson & Hodges, 1992; K.S. Graham, Hodges & Patterson, 1994). Surface dyslexia is a reading disorder characterised by a frequency-by-regularity interaction in accuracy of single-word oral reading. The majority of errors occur to lower-frequency words with atypical spelling-sound correspondences, and almost always take the form of 'regularised' pronunciations (pint pronounced to rhyme with "mint"; gauge pronounced "gawge", etc.). In contrast to the dual-route theory of reading, our view is that the association between semantic impairment and surface dyslexia is meaningful and causal. This account, developed over a number of years, is based on a connectionist model of word reading, not only in English (Plaut et al., 1996; Seidenberg & McClelland, 1989) but also in Japanese (Fushimi, Ijuin, Patterson & Tatsumi, 1999; Ijuin, Fushimi, Patterson & Tatsumi, 1999), in which the basic mechanism for translating a written word into a pronunciation is a network relying on learned correspondences between orthography and phonology at different sizes/levels. What is learned is not abstract symbolic grapheme-phoneme rules but rather connection weights based on statistical typicalities. Highly frequent orthographic sequences will be well learned by the network; and because knowledge about translation to phonology operates over both small and large chunks, words will be correctly and efficiently pronounced if they have either (a) typical component correspondences even if the whole word is not frequent (e.g. nave or cove), or (b) whole-word high frequency even if the component correspondences are not typical (e.g. have or move). Lower-frequency words with atypical correspondences, however, will not be well learned by this system, and thus something must counteract the tendency of the unimpaired network to produce regularised pronunciations of words like pint and gauge. Our hypothesis is that this additional source of word-specific constraint comes from word meaning, a part of the system already well established to differentiate between specific words. In the kind of interactive system that we postulate, meaning will be activated for all words, whatever their frequency or regularity characteristics; but this additional semantic activation will be especially important for error-free processing of the low-frequency exceptions. The hypothesis thus predicts that any serious disruption to semantics will lead to surface dyslexia, as it indeed seems to do in SD and other conditions mimicking it, such as the occasional traumatic brain injury causing severe left inferior temporal damage (Patterson & Behrmann, 1997). A more general version of this hypothesis suggests that all components of the ability to read (which is a late-acquired skill in the development of both the individual human child and the human species) are likely to depend on other cognitive functions, and thus that deficits in these reading components are always likely to be associated with disruption to other, earlier acquired functions. A case for a meaningful association of surface dyslexia with semantic deficits, of phonological dyslexia with malfunction of general language phonology, and of pure alexia with visual-processing deficits was made by Patterson & Lambon Ralph (1999).

As so often, AD requires a slightly more complicated story because semantic deterioration is only one part of the syndrome. Nevertheless, we have demonstrated a highly reliable increase in errors to lower-frequency irregular words as a function of the progression of AD, plus a striking increase in word-reading response times (RTs) over longitudinal assessments (Strain, Patterson, Graham & Hodges, 1998). When first assessed, our cohort of AD patients had average word-reading RTs equivalent to those of their age-matched controls (mean ≈ 650 ms for single-syllable words). About two years later (same patients, same words), correct reading responses to the three easiest word sets (high-frequency regular, low-frequency regular, high-frequency irregular) averaged around 860 ms, with correct RTs to the most difficult words (low-frequency irregular) even slower, ≈ 930 ms.

The ability to spell words to dictation receives the same treatment and prediction in our model, only more so, because the sound-to-spelling correspondences in English are even more unpredictable and one-to-many than spelling-to-sound correspondences for reading. The data support this prediction: all of the SD patients that we have studied have been surface dysgraphic, making many errors of spelling words as they sound (e.g. "giraffe" → jeraf, "tongue" → tung) (N.L. Graham, Patterson & Hodges, 2000); furthermore, this surface deficit is almost invariably revealed earlier and/or more severely in spelling than in reading. It is true that many normal adults are less skilled spellers than readers; but for some of our very dysgraphic SD patients we have evidence of excellent pre-morbid spelling. We were able to track spelling performance in FM, the profoundly anomic SD patient described above, for seven years (N.L.Graham, Patterson & Hodges, 2001). She started out as a pure surface dysgraphic case but, as her speech production and comprehension declined with SD progression, the 'control' of her spelling by phonology also loosened: at the end of this longitudinal study FM's responses in spelling to dictation bore virtually no relationship to what was dictated. The great majority of her productions were, however, still orthographically word-like and composed of letters in proportion to their frequencies of occurrence in the English vocabulary. These results demonstrate the preservation of bare bones orthographic knowledge, the production of which was no longer under any stimulus control.

M3.3 Verb inflections

M3.3.1 The impact of semantic impairment on inflecting verbs

The dual-mechanism (or "Words and Rules") account of language processes proposed by Pinker (1999) incorporates a symbolic rule system to deal with regular exemplars and an associative lexical memory to handle exceptions. In our contrasting connectionist account, a single complex procedure processes both regular and irregular items. Dissociations between success with these two classes are attributed to more general impairments in the semantic or phonological subsystems of language which, we claim, are unequally stressed by irregular and regular words. The arguments here are similar to those in reading, at least with regard to the impact of semantic impairment. That is, we predicted that SD patients would have a frequency-modulated selective difficulty with producing or recognising the correct past tense forms of irregular verbs, which they did (Patterson, Lambon Ralph, Hodges & McClelland, 2001: see Table 1 for their success in generating past-tense verb forms in a sentence completion experiment). The pattern of error types was especially consistent with the connectionist account, as was the fact that the degree of the irregular deficit across patients correlated with their performance on a synonym-judgement comprehension task on the same verbs. The slope of the function relating past-tense production to comprehension was 0.88 for the 50 irregular verbs and 0.08 for the 50 regular items.

Table 1: Mean percent correct for SD patients (n=8) in generating the past-tense forms of high- and low-frequency regular and irregular verbs.

	High Freq	Low Freq
Regular	98	96
Irregular	71	53

M3.3.2 The impact of phonological impairment on inflecting verbs

Although the research described next does not address the issue of the impact of semantic deficits on language processing, it seems sensible to include our investigation of the other side of the verb inflection issue here. Pinker's (1999) model predicts that the rule system responsible for the regular –ed inflection should be independently vulnerable to disruption by brain injury. Ullman, Pinker and colleagues (Ullman et al., 1997) published data demonstrating that one patient with Broca's aphasia was dramatically better at generating the past-tense of irregular than regular verbs in a sentence completion task, and that a larger number of similar patients who were too impaired to perform the generation task showed the irregular > regular pattern in reading past-tense verb forms. Our account of this side of the putative dissociation invokes phonological processes, with which Broca's aphasics have substantial difficulties. Compared to irregular past-tense verbs, regular past-tense forms are on average more phonologically complex (indeed, in an analysis by Burzio, 2002, they are frankly phonologically irregular) because they contain terminal consonant clusters like /vd/ and /gd/ (as in "loved" and "dragged") that never occur in irregular past-tense forms and indeed never occur in any words in English apart from past-tense regular verbs. In a study of 10 Broca's aphasic cases (Bird, Lambon Ralph, Seidenberg, McClelland & Patterson, in press), we demonstrated a significant irregular > regular advantage in three production tasks (sentence completion, repetition and reading) using materials like those in Ullman et al. In a subsequent experiment where we matched the consonant-vowel structure of regular and irregular past tense forms, the discrepancy in performance for these same patients completely disappeared in sentence completion and repetition. A remaining irregular advantage in reading was attributed to concreteness effects. Our interpretation of this and other evidence (McClelland & Patterson, in press) is that there is no compelling demonstration of an augmented deficit in producing the regular past tense that cannot be attributed to a phonological source.

M3.4 Auditory-verbal working memory (AVWM)

In our earlier research, we demonstrated that three SD patients, all with normal digit span and thus no prominent deficit in AVWM, had a high rate of phonological migration errors in immediate serial recall (ISR) of sequences of 3-4 unrelated words (Patterson, Graham & Hodges, 1994). For example, a sequence like "pencil, chicken, sword" might be repeated back as "sencil, sicken, pord". Lists for ISR were constructed for individual patients, with each list composed exclusively of words that were either 'known' or 'degraded' for that patient. So-called 'known' items were words that the patients could either still name from a picture, if they were concrete concepts, or words that they were still using appropriately in spontaneous speech; 'degraded' items were words that the patients failed to name and also failed to process correctly in word-picture matching or synonym judgement tasks. The fact that most of the ISR errors occurred to 'degraded' words, even with the two sets matched as closely as possible for factors such as word frequency, suggests that semantic knowledge about a word plays some important role in binding its phonological features, especially under conditions of high AVWM load. This phenomenon and hypothesis, and an extension of it to repetition of a single word after a short filled delay, were explored further in PhD research by Raymond Knott (Knott, Patterson & Hodges, 1997; 2000). These deficits may also be germane to our recent observations of poor word-list learning in SD. In a study in which lists of words (selected individually for each of seven patients as 'known' or 'degraded') were presented three times each (in different orders) and followed by free recall after each presentation, the patients' performance displayed a significant advantage for 'known' > 'degraded' but was sub-normal even for 'known' words (K.S. Graham et al., 2002). As in the ISR paradigm, they made many phonological blend errors on 'degraded' words.

M3.5 Non-Fluent Progressive Aphasia

Progressive aphasia comes in two main syndromes or patterns: fluent but anomic speech associated with temporal-variant Pick's disease (SD), and nonfluent speech with phonological and syntactic abnormalities. The latter, known as non-fluent progressive aphasia (NFPA), appears to arise from several different degenerative aetiologies, principally (at least in our case series) AD (Croot, Hodges, Xuereb & Patterson, 2000) or corticobasal degeneration (N.L. Graham, Bak, Patterson & Hodges, submitted). Our work has concentrated far more on the fluent syndrome: apart from some basic comparisons of the main presenting features of the two syndromes (e.g. Hodges & Patterson, 1996; Patterson et al., in press), our published research on NFPA to date has consisted mainly of the work by Karen Croot, who was a PhD student with our group from 1994-1998. As well as characterising a number of cases of the atypical nonfluent aphasic presentation of AD (Croot et al., 2000), she studied word production by four patients with NFPA (Croot, Patterson & Hodges, 1998; Croot, Hodges & Patterson, 1999a) with the goal of relating their impairments in single-word production tasks like picture naming, word repetition and word reading to an interactive spreading-activation model of normal and impaired speech production (Dell, Schwartz, Martin, Saffran & Gagnon, 1997). This model has two independently manipulable parameters: the strength of the connections between nodes in the network, and the rate at which activation in the network, once initiated, decays. Abnormality in either of these parameters disrupts speech production; but the aphasic profiles associated with the two should be distinct with respect to severity of impairment in different speaking tasks (e.g. naming objects vs. repeating spoken words), error types, and other features. We observed examples of both aphasic profiles amongst our NFPA cases. Intriguingly, two cases representing one example of each type were brothers who subsequently came to post-mortem examination and were shown to have markedly different distributions of atrophy in peri- and extra-sylvian left-hemisphere regions.

M3.6 Summary

Our research on language has led to the hypothesis that semantics and phonology (and their interaction) are central to all aspects of language processing, and that essentially every pattern of language disorder can be traced back to disruption in one or other of these fundamental systems. Most of our research in the last quinquennium has concentrated on the wide-ranging impact of semantic disruption which – harking back to M1 – yields language performance dominated by typicality. This pattern of greater vulnerability for words with atypical transformations from spelling to sound, or stem to past tense, etc, is in essence an exaggeration of the normal pattern of processing. Phonological disorders, on the other hand, produce a more complicated range of language impairments. The incorporation of neuroanatomical hypotheses into our processing models, particularly that the semantic system is bilaterally represented but that phonology is left-lateralised, significantly improves success in capturing the range of impaired language performance.

AWARDS AND HONOURS

John Hodges:

• elected President of the British Neuro-Psychiatric Association 1998

• elected President of the World Federation of Neurology, Research Group on Aphasia and Cognitive Disorders 1998

• appointed Director of the Alzheimer's Research Trust Centre for Cambridge 1998

• elected Fellow of the Academy of Medical Sciences 2002

Karalyn Patterson:

• elected International Fellow of the American Psychological Society 2001

• nominated Fellow of the Academy of Medical Sciences (election 2003)

• keynote lecturer for the International Congress on Spoken Language Processing, Beijing, 2000

Kim Graham:

• elected member of the Memory Disorders Research Society 1998 (limited to 100 members internationally)

• invited speaker at the Royal Society of Edinburgh 2002

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TRANSFER TO HEALTH SERVICE

Contributions of the DMS group to the Health Service come in two forms:
(a) Like other MRC-CBU Research Groups, we are continually developing cognitive assessments that are subsequently adopted for use in Memory Disorder and Speech Therapy Clinics. One of the most important of these in recent years is the ACE (Addenbrooke's Cognitive Examination: Mathuranath, Nestor, Berrios, Rakowicz & Hodges, 2000), based on the universally used Mini-Mental State Examination but in an expanded format that enables improved differentiation of various types of dementia.
(b) People who care for sufferers of the more prevalent forms of dementia (especially Alzheimer's Disease) receive substantial support from organisations like the Alzheimer's Disease Society. Those who care for individuals with less common but equally distressing forms of dementing illnesses, like frontotemporal dementia (FTD), have no comparable source of information and support. The DMS research group therefore organises an FTD support group that meets at the CBU approximately 4 times/year. At each meeting, we provide a special speaker, either from within our group or outside, on a topic of importance to carers of these patients; and the carers then have the opportunity to talk both to us and to each other about their concerns. A newsletter is produced and sent to those who attend and all those unable to attend the meeting.

EXTERNAL GRANTS

1. National Institutes of Mental Health (USA) Programme Grant. Toward a model of normal and disordered cognition. 1.3.97 to 28.2.02. Total: £149,275 (KP) (NB this is the CBU portion of a much larger grant for a consortium of researchers led by Prof J L McClelland)
2. Alzheimer's Research Trust Centre Grant. 1.8.98 to 31.7.03. Total: £75, 000. (JRH)
3. MRC Programme Grant. The early diagnosis, differentiation and clinical course of dementia: Alzheimer's, frontotemporal and vascular types. 1.10.98-30.09.03. Total: £845, 000. (JRH)
4. MRC Training Fellowship (for Dr Sian Thompson). The neural basis of autobiographical and semantic memory. 1.4.00 to 31.3.03. Total: £105, 000 (JRH)
5. PSP Association Project Grant. Clinical and neuropsychological studies of PSP. 1.4.00 to 31.3.02. Total: £40, 000. (JRH/TB)

6. Alzheimer's Research Trust Ph.D. studentship (for Ms Fiona Clague). The early diagnosis of AD and related dementias using tests of people naming and cross-modal associative learning. 1.10.01 to 30.9.04. Total: £57, 000. (KG/JRH)

7. Wellcome Research Training Fellowship (for Dr Andrew Graham). Memory in frontotemporal dementia and the role of the ventromedial frontal cortex. 1.12.01 to 30.11.04. Total: £180, 165. (KG/JRH)

8. Wellcome Research Training Fellowship (for Dr Rhys Davies). The neural basis of semantic memory impairment in Alzheimer's disease and Fronto-temporal dementia: A pathological and in vivo study. 1.3.02 to 28.2.05. Total: £170, 000 (JRH)

9. Alzheimer's Research Trust Programme Grant. The functional contribution of medial temporal lobe regions to profiles of memory impairment in dementia: An interdisciplinary approach using neuropsychological and neuroimaging methodologies. 1.10.02 to 30.9.07. Total: £690,000. (KG/JRH)

10. National Institutes of Mental Health (USA) Interdisciplinary Behavioural Science Centre Grant. Toward a neurobiologically constrained framework for modelling human cognition. 1.10.02 to 30.9.07. Total: £158,040 (KP) (NB this is the CBU portion of a much larger grant for a consortium of researchers led by Prof J L McClelland)

11. Sarah Matheson Trust. PSP and multiple system atrophy. 1/8/02-30/04/04. £7,118

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6 MEMORY AND KNOWLEDGE: REHABILITATION SECTION PROGRESS REPORT

Overview

This programme, focused on the neuropsychological rehabilitation of memory and learning disorders, operates at the interface between clinical practice and academic research. The research projects in this programme reflect a balance between theoretically based experimental work and clinically driven therapeutic research. The patient groups studied are primarily those with cognitive problems resulting from non-progressive brain damage particularly traumatic brain injury, encephalitis, hypoxic brain injury and stroke.

The research conducted under this programme has resulted in changes in rehabilitation procedures throughout the United Kingdom, North America and Australia. Errorless learning for the rehabilitation of people with memory problems is now a widely accepted strategy by therapists and psychologists. Neuropage is another example of research influencing clinical practice. Following our studies in Cambridge and Ely, brain injured people throughout the United Kingdom can now access the paging service to help them be more independent in their daily lives. Our new tests have also changed neuropsychological assessment practice worldwide. We have focussed on ecologically valid tests that will predict everyday problems arising from cognitive impairments. Our tests of memory, unilateral neglect and executive functioning are used throughout the world and have been translated into several languages. More recently a test to monitor recovery from severe head injury, The Wessex Head Injury Matrix, is proving to be a useful clinical and research tool. It is one of the main measures in our collaborative study with Pickard and others at Addenbrooke's Hospital looking at the relationship between behavioural recovery and changes in the brain as measured by PET scans

A crucial component of the programme and an illustration of how research and clinical practice are interlinked is the working relationship established with Oliver Zangwill Centre for Neuropsychological Rehabilitation. The centre opened in September 1996 as a result of a collaborative work between the MRC, the (former) Lifespan NHS trust, Anglia and Oxford Research and Development Initiative. The cognitive rehabilitation programme at the centre, aimed at patients with non-progressive brain injury aged between 16 and 65 years, allows a two-way transfer of findings from scientific research and clinical practice. We are able to implement findings from psychology and allied sciences within a health service context that, in turn, provides suitable patients and an appropriate environment for both group and single case studies designed by cognitive and clinical psychologists and neuroscientists. We have introduced rehabilitation therapies that have been designed from a theoretical basis, and evaluate their effectiveness in terms of rehabilitation outcomes. Thus, the Oliver Zangwill Centre (OZC) offers a substantial and perhaps unique capacity to evaluate theoretical models.

One example where two research studies have led to a new clinical service based at the OZC is the introduction of Neuropage. This uses a simple and portable paging device, with a screen, that can be attached to a belt worn by the patient. The system uses an arrangement of microcomputers linked to a conventional computer memory, and by telephone, to a paging company. The scheduling of reminders for each individual is entered into the computer and, from then on no further interfacing is necessary. On the appropriate date and time NeuroPage accesses the user's data files, determines the reminder to be delivered and transmits the information. A pilot study (Wilson, Evans, Emslie, & Malinek, 1997); two single case studies (Evans, Emslie, & Wilson, 1998) and (Wilson, Emslie, Quirk, & Evans, 1999) and a randomised control study (Wilson, Emslie, Quirk, & Evans, 2001) demonstrated that NeuroPage significantly reduces the everyday memory and/or planning problems of people with brain injury. As a result of this research, East Fenland Primary Care Trust (formerly Lifespan NHS) now runs NeuroPage as a commercial service.

Our studies of errorless learning which form part of project M5 have also resulted in changes in clinical practice. Errorless learning is a teaching technique whereby people are prevented, as far as possible, from making mistakes while learning a new skill or acquiring new information. Earlier work by Wilson and Baddeley demonstrated the superiority of errorless over errorful learning for people with severe memory disorders following non-progressive brain injury. A series of studies by Wilson and Clare in collaboration with Hodges has demonstrated that errorless learning is a useful method for teaching practical, everyday information to people with dementia of the Alzheimer type (Clare, Wilson, Breen, & Hodges, 1999; Clare et al., 2000; Clare, Wilson, Carter, Hodges, & Adams, 2001). In some instances, information taught is well retained at 1 - 3 years follow-up despite the fact that the disease is progressing. Potentially this is an important clinical finding suggesting that some practical information can be taught in the early/moderate stages of Alzheimer's disease that can be retained (possibly with practice) when the disease progresses and could enable people with dementia to remain for longer outside institutional care. Psychologists and therapists working in memory rehabilitation for people with non-progressive conditions routinely apply errorless learning approaches when teaching new skills or new information to their brain injured clients.

Prior to any treatment patients require a detailed assessment. One of the most crucial components of scientific research is the sensitivity, validity and reliability of the tools for measurement. Measurement instruments fulfilling these criteria are often difficult to establish in the field of cognitive neuroscience where the underlying processes are poorly understood. Furthermore, tests developed in the laboratory often bear little relationship to the ways in which these underlying processes - like various forms of memory - are actually used in the service of real-life, everyday behaviour. For several years Wilson has been involved in the development of ecologically valid tests to predict behaviour outside the laboratory or clinic. The Rivermead Behavioural Memory Test (Wilson, Cockburn, & Baddeley, 1985), for example, is a good predictor of likely success in employment or independent living but is less good at detecting subtle or mild memory deficits. Consequently, a more probing version of the test (Wilson, Clare, Baddeley, Cockburn, Watson and Tate, 1999) has been developed and published.

In addition to tests for people who are fully conscious, we have also been working with patients in states of reduced awareness following severe head injury. As patients emerge from coma, recovery is usually monitored using simple checklists of behaviours and skills. Using neuroimaging, electrophysiology and behavioural assessment we have investigated links and preliminary results show very promising relationships between behaviour and neurometabolic coupling – a result that has enormous implications both theoretically in terms of theories of recovery and clinically in terms of neuroprotection and prediction of outcome.

In a second project we investigated brain function in people who are in the vegetative state or who are minimally conscious for signs of covert cognition. Results are being analysed on a single case basis and to date, have confirmed results of behavioural evaluation

Project M5: Theoretically derived treatment techniques for cognitive disabilities following brain injury

Scientific Direction: Wilson (40%), Shiel (25%)

Grant supported scientists Emslie (20%), Greenfield (5%)

Research support Clare (60%), Hawkins (45%), Carter (50%), Foley (25%).

M5.1 Errorless learning

The main theoretical issue explored over the past five years is whether errorless learning is primarily dependent on implicit memory (as suggested by Baddeley & Wilson 1994) or explicit memory (as suggested by Squires, Hunkin, & Parkin, 1997) or a combination of both of these mechanisms. In collaboration with Norris and Page, we designed an experiment to help answer the question. We tested people with very severe memory impairment and people with moderate memory impairment on both errorless and errorful learning and on both implicit and explicit recall. We made three predictions:

1. If errorless learning depended on implicit memory, then both the severely impaired and moderately impaired people should benefit from the implicit-errorless learning condition as both groups are able to use implicit memory.

2. If errorless learning works by capitalising on residual explicit memory, then those with some episodic memory functioning (i.e. the moderately impaired people) will benefit from the explicit-errorless learning condition more than those with no/very little episodic memory functioning (i.e. the severely impaired group).

3. If both explanations were correct, then we would expect the severely impaired group to benefit from errorless learning only under the implicit-errorless learning condition, whereas those with some episodic functioning will benefit from both errorless learning conditions.

In addition we gave two recognition memory experiments and a source memory experiment. As well as asking participants to recognise target words from novel words, we wanted to see if they could recognise their own errors. In the source memory experiment two sets of words were presented and participants had to decide either how pleasant or how imageable the word was. Later, they were required to recognise whether each word had been presented earlier and if a response was yes, they had to say whether the word was in the pleasant or the imageable list.

Two separate experiments confirmed that errorless learning is superior to errorful learning under implicit memory conditions. This is true both for those with severe memory impairment and for those with moderate memory impairment.. Thus our first prediction was born out. Our second prediction was that if residual explicit memory was the reason then the moderately impaired group (i.e. those with some episodic memory functioning) will benefit more from the explicit errorless learning than the severely impaired group. The results were less clear cut here but the severely impaired group scored marginally better than the moderately impaired group. The third prediction was that if both explanations were correct then the severely impaired group would benefit only under the implicit and not the explicit errorless conditions whereas the moderately impaired group would benefit under the implicit and explicit conditions. This was not true. The severely impaired group benefited under both the implicit and explicit conditions (probably because they used implicit memory regardless), whereas the moderate group showed no difference in Experiment 2 between the errorless and errorful conditions.

The major point of interest from the recognition tasks is that both severely and moderately memory impaired people have difficulty discriminating between target words and their own self generated errors. Again, once an error is introduced into a damaged episodic memory system, it is hard to distinguish the error from a correct response. In turn, this is likely to mean errors are difficult to eliminate in real life situations, so trial-and-error learning should be avoided.

Finally, confirmation in support of errorless learning is provided, indirectly, from the source memory tasks. Participants, at least to some extent, were able to tell if they had encountered a word before, but they were poor at knowing whether it had come from the pleasantness rating list or the imageability list. In practice, this means that information can be learned but memory impaired people cannot tell where they learned the information. The link with errorless learning is that here too, information can be learned, but without an adequate episodic memory system, incorrect information will not be rejected as the sources of the correct and incorrect information cannot be distinguished.

M5.2 Compensatory memory aids

In addition to errorless learning we are interested in compensatory memory aids. We have been involved in both modifying technology and in identifying variables that predict use of memory aids. The very successful NeuroPage studies have been described above. These studies were funded by the National Health Service Research and Development Initiative. One ongoing study, also based at the OZC and funded by the Private Patients Plan, is a collaborative project with Newell and Gregor at the University of Dundee. This project 'Memojog' involves the design and evaluation of an electronic organiser that avoids some of the limitations of NeuroPage. It is an interactive system with a two-way transfer of messages that allows the individual users more control, since they can enter their own messages. We are also investigating the possibility of a voice-operated system.

A completed study was carried out in collaboration with Wright (Cardiff) on another NHS R&D grant. We compared two kinds of palmtop/electronic organisers. We found that high frequency users preferred the organiser with a key board whereas low frequency users made more entries using a stylised pen. This means essentially that different clients have different preferences but those who are likely to use their organisers a great deal will probably prefer to use one with a key board while those who only use their organisers occasionally are likely to prefer one requiring a stylised pen.

Another study was a survey carried out with funding awarded to Evans, Wilson and Brentnall, from the NHS R&D to look at which memory impaired people make good use of memory aids. This was carried out to determine the accuracy of a theoretical framework proposed in 1996 by Wilson and Watson (1996). The latest survey (Evans, Wilson, Needham, & Brentnall, in press) having found support for the Wilson and Watson framework also identified further variables that best predict use of memory aids. Interviews were conducted with 101 people with memory problems resulting from brain injury and their carers. Use of memory aids correlated with overall level of independence (as in the Wilson and Watson study). The variables that best predicted use of memory aids were 1) current age, 2) time since injury (this was different from the previous study), 3) number of aids used premorbidly, 4) a measure of attentional functioning. The last mentioned was not measured in the earlier study .

M5.3 Issues in Cognitive Rehabilitation

Cognitive rehabilitation is a complex field that should address the social, behavioural and emotional difficulties that often accompany the cognitive deficits consequent upon brain damage. Colleagues at the OZC particularly Evans and Williams (now at the University of Exeter) have been instrumental in combining cognitive remediation strategies with cognitive behaviour therapy (CBT). Although CBT is one of the best validated approaches for dealing with emotional disorders, it has only recently been used for people with brain injury. Williams, Evans, & Wilson (in press a) describe its successful use with this client group. Williams, Evans, Wilson, & Needham (in press b) also report on the prevalence of post traumatic stress disorder in a community sample of people with non-progressive brain injury.

In a major recent publication, Wilson (2002) has provided a provisional model of cognitive rehabilitation in which she attempts to synthesise a number of different models that have influenced the field. These include models of cognition, emotion, behaviour assessment and recovery. The two basic assumptions are that (1) neuropsychological rehabilitation is concerned with the amelioration of cognitive, social and emotional deficits caused by an insult to the brain and (2) the main purposes of such rehabilitation are to enable people with disabilities to achieve their optimum level of well being, to reduce the impact of their problems on everyday life and to help them return to their own, most appropriate environments. From this it follows that no one model, theory or framework can deal with all the difficulties facing people with brain impairments. These often include multiple cognitive impairments as well as accompanying social, emotional and behavioural problems. Those engaged in neuropsychological rehabilitation should draw on a number of theoretical approaches in order to address the functional, everyday problems that people with brain injury and their families try to overcome. Of the many theories that impact on rehabilitation, four areas are, perhaps, of particular importance: namely theories of cognitive functioning, emotion, behaviour and learning. These are incorporated into Wilson's provisional model. Consideration is also given to theories of assessment, recovery and compensation.

Project M6: New assessment procedures for identifying and monitoring cognitive deficits.

Scientific direction: Wilson (35%), Shiel (25%)

Grant supported scientists: Emslie (80%), Greenfield (90%)

Research support: Clare (30%), Hawkins (45%), Carter (50%), Foley (50%).

A major focus of the research group has been to develop new and better procedures for assessing and identifying cognitive deficits. In doing this, we have focussed on ecologically valid tests that will predict everyday problems arising from cognitive impairments. The resulting tests of memory, unilateral neglect and executive functioning have changed neuropsychological assessment practice worldwide. The major areas of test development are summarised below.

The Extended Rivermead Behavioural Memory Test developed in collaboration with Tate at the University of Sydney was published in 1998. This test was designed to avoid floor and ceiling effects and thus detect subtle memory impairments in both non brain injured and brain injured people. Unlike the original RBMT, the Extended RBMT includes faces of European, African and Asian origin and is more suitable for use in multicultural societies. The sample used to standardise and norm the test also included people from European, African and Asian backgrounds. A study carried out with 45 neurologically impaired people who were given the original and extended versions, in counter balanced order, separated those with reasonable scores on the easier, original version into good, average, poor and impaired subgroups on the more difficult, later version. One further modification is the option of a model route for those people unable to complete the real route to assess learning of a new route.

A further test that we have been working on over the past five years is the Cambridge Prospective Memory Test. This is nearing completion. Prospective memory involves remembering to do something at the right time, or within a certain interval or when a certain event occurs. The most common memory complaints are connected to with failures of prospective memory yet this aspect of memory function is rarely assessed formally. The RBMT and the Extended RBMT both contain some prospective memory tasks but there was a need for a more clinically sensitive, ecologically valid test of prospective memory. A pilot study was carried out with Groot, a visiting Dutch student, (Groot, Wilson, Evans, & Watson, 2002). Further work modified the pilot version before collection of norms on a non brain injured population and a group of brain injured people. To date we have seen about 180 controls and 30 people with brain injury. As usual we have had problems tracking down control participants who are of below average intellectual functioning. Collaboration with Mockler in Colchester and McCarthy and Kingsley in London promises to rectify this situation and we plan to complete this test by early 2003.

Another successful, ecologically valid test influenced by two theoretical models - the Working Memory Model (Baddeley & Hitch, 1974) and the Supervisory Attentional System Model (Norman & Shallice, 1986) - is the Behavioural Assessment of the Dysexecutive Syndrome (BADS) (Wilson, Alderman, Burgess, Emslie, & Evans, 1996). The BADS is a useful measure both for people with brain injury and for people with schizophrenia. Following several requests for a children's version of the BADS and a grant from the NHS R&D, Emslie and

Wilson in collaboration with Colin Wilson from Belfast and Burden from Cambridge, have modified the adult version of the BADS to make it suitable for children. We have collected norms on 262 children aged 8-16 from mainstream schools and a group of more than 60 children with neurological problems. The test should be completed by the end of 2002.

Wilson and Evans were recently awarded a grant from the NHS R&D to develop measures to assess divided attention deficits in people with brain injury. It is not uncommon for people with brain injury to complain that they cannot do two things at the same time (e.g. "Don't talk to me while I am walking as I can't concentrate."). With Greenfield we have begun piloting a series of tests that involve (a) a single cognitive task, (b) a single motor task, (c) dual cognitive tasks, (d) dual motor tasks and (e) dual cognitive and motor tasks. We have given these tasks to patients and controls and, following further modifications, we are ready to collect norms on them. Not only should we produce a sensitive, reliable and valid test of divided attention, at the completion of this study but we should also be in a position to plan a treatment study to try to reduce deficits of divided attention.

Project M7: Predicting Recovery from Brain Injury

Scientific Direction: Shiel (50%), Wilson (25%)

Grant supported scientists: Greenfield (5%)

Research support Clare (20%), Hawkins (10%), Foley (25%).

In collaboration with Dr A Owen (CBU), Prof JD Pickard and Mr L Gelling (Dept of Academic Neurosurgery), Prof DK Menon (Neurosurgical Critical Care unit [NCCU]), Dr T Fryer (Wolfson Brain Imaging Centre [WBIC]), Dr S Boniface and Dr M Coleman (Department of Neurophysiology), Ms L Hooper and Ms L Elliott (Physiotherapy Department) Ms R Jackson (Occupational Therapy Department) , we are carrying out a series of studies to determine (a) which early behaviours following coma predict outcome and (b) whether behavioural changes mirror changes seen in brain activity as measured by PET imaging and electrophysiology.

These studies began in December 1999. The first study examines changes in behaviour, changes in regional cerebral blood flow (rCBF) and changes in electrophysiological measures (EEG) and transcranial magnetic stimulation (TMS) during and immediately after coma. To date 12 patients have been entered into the first part of the study and two patients rescanned after coma. Preliminary results show that there is a 50 per cent decrease in overall rCBF during coma. It is possible that an association exists between neurometabolic coupling (EEG and PET) and scores on the Wessex Head Injury Matrix (WHIM) both at the time of scanning and one month later. Further data are required, however, to support both of these preliminary findings. This study stimulated a further piece of research looking at the effects of posture on arousal. A grant proposal has been submitted to fund a research physiotherapist for a period of two years to investigate this more systematically. Preliminary results of a single case study have been presented (Crossley et al 2002) and two papers and a symposium are in preparation.

A second strand of the research is examining patients diagnosed as being in the vegetative state in order to compare behaviours as measured on the WHIM with patterns of brain activation and electrophysiology. Assessment and diagnosis of the vegetative state is traditionally determined by behavioural observation alone.

The relationships between PET activation in response to familiar faces and words, electrophysiology and behavioural observations are being investigated. The aim is to illuminate the relationship between these observations and the other measures, which should ultimately lead to more accurate diagnosis. To date, three patients have been scanned but scanning had to be abandoned in two further cases due to patients' movement. This has led to the protocol being re-written in order to allow sedation during the scans. Collaboration in this project is being developed with the Rehabilitation Hospital in Leamington Spa, which specialises in treating patients who are vegetative or minimally conscious. This will facilitate further recruitment and ensure that a significant number of patients diagnosed as vegetative are recruited to the study. At present we scan one patient every month.

The third aspect of this programme is concerned with post-traumatic amnesia. Previous work by Wilson et al (Wilson, Baddeley, Shiel, & Patton, 1992; Wilson, Evans et al., 1999) has demonstrated that patients in PTA have a wide range of deficits in addition to problems of memory and orientation and that emergence from PTA is a gradual change rather than an all or nothing event. A new test of PTA has been developed and data collection has begun. There are eight parallel forms of the test and data on parallel form reliability with controls has also started.

AWARDS AND HONOURS (since 1997)

1996-1998 Chair of British Neuropsychological Society

1998 Awarded an OBE in New Year's Honours List for Services to Medical Rehabilitation

1998-1999 Vice-Chair of United Kingdom Acquired Brain Injury Forum

2000 Awarded The British Psychological Society Award for Distinguished Contributions to Professional Psychology

2001 Fellow of the Academy of Medical Sciences

2001 Fellow of the Academy of Learned Societies for the Social Sciences

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Translations

Books

Clinical Management of Memory Problems: Japanese (1997).

Behavioural Assessment of the Dysexecutive Syndrome: Dutch (1997), Portugese (1999), Swedish (1999), German (2000), Danish (2001).

Selecting and Interpreting and Administering Cognitive Tests: Japanese (1999).

Coping with Memory Problems: Japanese (1999).

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TRANSFER TO HEALTH SERVICE

a) Tests developed and used for neuropsychological assessment in the Health Service

1996 Wilson, B. A., Alderman, N., Burgess, P., Emslie, H., & Evans, J. (1996). Behavioural Assessment of the Dysexecutive Syndrome. Bury St Edmunds, Suffolk: Thames Valley Test Company.

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b) Transfer of research into the Health Service

Our studies evaluating NeuroPage (a paging system to reduce the every day memory problems of people with neurological impairments) resulted in Lifespan Health Trust setting up a commercial service for people through the United Kingdom.

Our studies evaluating Errorless Learning have resulted in this technique becoming a well established procedure in memory rehabilitation.

The Oliver Zangwill Centre for Neuropsychological Rehabilitation is an internationally recognised centre of clinical excellence. It is a centre which enables findings from research to be applied in a clinical setting and findings from effective treatment to confirm theoretical interpretations.

EXTERNAL GRANTS

From the Department of Health Research and Development (joint holder) £73,813 for a project entitled "Reliability and validity of assessment procedures after head injury" - PCD/A3/67 (D. L. McLellan, B. A. Wilson, A.M. Shiel, J.S. Burn - 12 months).

From the Department of Health Research and Development (joint holder) £40,075 for a project entitled "Development of assessment scales for severely brain injured children" - PCD/A3/66 (D. L. McLellan, B. A. Wilson and A.M. Shiel - 12 months).

From the Department of Health Research and Development ((joint holder) £300,107 for a project entitled "A controlled evaluation of intensive therapy after head injury" - PCD/A1/ (D. L. McLellan, B. A. Wilson, A.M. Shiel and J.S. Burn)

From the Anglia and Oxford Regional Health Authority (joint holder) £46,588 for a project entitled

"Effectiveness of memory therapy based on errorless learning" - HSR/ADH/1095/65 (B. A. Wilson, J. Hodges, K. Breen - 18 months from 1/1/96).

From the NHS Executive Anglia & Oxford (joint holder) £40,820 for a project entitled "Which memory impaired people make good use of compensatory strategies" (J. J. Evans, B. A. Wilson and S. Brentnall).

From the NHS South & West R&D Programme for Physical and Complex Disabilities (joint holder) £93,127 for a project entitled "Helping people with memory impairments recall facts and procedures - a comparison of two computer aids for personal information management" - PCD2/A1/215 (P. Wright, B. Wilson, J. Evans, H. Emslie). (2 years from 1/10/96)

From the Anglia and Oxford R & D (joint holder) £79,580 for a project entitled "The evaluation of a paging service for people with brain injury" - HSR-LHT-1196-90 (B. A. Wilson, J. J. Evans, H. Emslie and J. Appleby) (2 years from 1/1/97)

From the Anglia and Oxford R & D (joint holder) £77,241 for a project entitled "The development and standardisation of an ecologically valid test for assessing children and adolescents with a dysexecutive syndrome" - HSR/0500/11 (H. Emslie, B A Wilson, C. Wilson & V. Burden) (30 months from 1/7/00).

From the Anglia and Oxford R&D (joint holder) £99,058 for a project entitled "Identifying and understanding divided attention deficits in people with brain injury" - HSR/0301/6 (B A Wilson & J J Evans) (3 years from 1/10/01).

From the Research Grants Council of Hong Kong (joint holder) HK$592,500 for a project entitled "Evaluating the effect of an on-line computer-assisted cognitive rehabilitation programme" - PolyU 5291/01M (Dr Tam Sing Fai, Dr Man Wai Kwong, Prof. David Watkins, Prof. Barbara A. Wilson, & Prof. Christina W.Y. Hui-Chan) (3 years from1/11/01).

Submitted to Remedi (joint application): An investigation into the cognitive and motor benefits of standing head injury patients upright in the critical care environment and thereafter (A. Shiel, L.Hooper, B.A. Wilson, V. Sparks, D. Menon, J. Pickard)

From the NHS (R&D), £58,189. PhD Studenthsip for Veronica Dobler, The role of attention in rehabilitation of childhood hemipoegia.

PRINCIPAL COLLABORATORS

The Oliver Zangwill Centre, Ely; The Ministry of Defence, Catterick;

Addenbrooke's Hospital; Wessex Neurological Centre, Southampton; the Royal Star & Garter Home, Richmond; Headway House, Cambridge; The Sue Ryder Home, Ely; Rehabilitation Studies Unit, University of Sydney; Department of Physical Medicine and Rehabilitation, Baylor College of Medicine, Houston.

7 METHODS RESEARCH AND INFRASTRUCTURE GROUP PROGRESS REPORT

Overview

The proposals for the CBU's programme in the period 1998-2003 made only a brief mention of the support that the research programmes need in the application of scientific methods derived from a range of disciplines, pointing to the established in-house statistical and mathematical consultancy service, which is still provided by two statisticians (Nimmo-Smith, Watson).

Over the last four years, however, the dramatic growth of Unit research activity based on electrophysiological measurements (EEG, MEG) and on brain imaging techniques (fMRI, MRI, PET) has brought about an equally vigorous growth in high-level methods support and research in these new areas. Staff with appropriate expertise have been recruited during the review period, some to support particular programmes of research (Brett, Cusack, Hauk), as well as a senior MRI physicist (Schwarzbauer), and in turn their help has been sought by the wider CBU community. This has led to a large increase in methods research and infrastructure activity, as documented in the following progress report. The range and the quality of the methods support being provided illustrates the effectiveness of the Unit's response, during the current quinquennium, to the challenge of developing convincing scientific programmes in technically demanding fields such as functional neuro-imaging.

In order to consolidate this growth in high-level methods research and general support, we have decided to form a fifth Unit grouping, with the title, as above, of Methods Research and Infrastructure Group. Ian Nimmo-Smith will provide overall leadership and co-ordination, with Christian Schwarzbauer responsible for MRI physics support and development, and Matthew Brett co-ordinating a wide range of imaging methods activities. This will allow greater managerial clarity in evaluating and structuring the Unit's methods activities, while providing a common focus for the varied methods activities that are now flourishing in the Unit. It will also provide a more coherent cost centre to which methods resources can be directed. However, it is not intended that the Methods group should be independently scientifically evaluated at the five-yearly review. The existence of the Methods resource remains justified in terms of the scientific programmes that it supports.

The progress report that follows describes the work of the CBU Methods community over the review period and gives details of several significant outputs from their work. These are grouped thematically to reflect the need for development of appropriate methods to support the full lifecycle of projects in the scientific programmes, from initial design and data collection through to analysis, modelling and publication.

General statistical and imaging support: The general statistical support service provided by Nimmo-Smith and Watson has helped to ensure the high quality and high level of acceptances for publication of work done at CBU. Several hundred consultations are made annually requiring a very broad spectrum of expertise. Queries can range from the relatively straightforward to ones which need more extensive investigations, trawls through the technical literature and assimilation of novel techniques, sometimes leading to co-authorship of papers. Some of these collaborations may lead to studies where the statistical or methodological issues predominate; in some there was an explicit collaborative partnership from the outset and the methodological issues have been determining factors in the eventual direction of the scientific enterprise.

The move towards using imaging techniques has called for the rapid assimilation of technically and conceptually demanding new expertise, resulting in successful collaborations, and the provision of higher level methodological support for imaging specialists. Imaging data and analysis software are complex, and the range of questions that have been asked of the data continue to expand; this has required considerable day-to-day support by the CBU Methods Group to researchers in the CBU and the Cambridge imaging community. The CBU methods team also provides regular and formalized feedback to researchers on methodological aspects of imaging experiments, via the imaging methods meetings and imaging management committee.

In-house training on topical issues in statistics and in brain imaging is provided through regular internal seminars, and information is made available through the CBU websites http://www.mrc-cbu.cam.ac.uk/Imaging and http://www.mrc-cbu.cam.ac.uk/Statistics.

Running experiments in the MRI scanner (MR1): Imaging experiments require the integration of techniques for presenting stimuli and recording behavioural responses with the complex and noisy environment of the MRI scanner. Various complex problems to meet the demand for accurate timing have been resolved (MR1.1), and there is now the ability to use recorded spoken responses effectively despite the low signal to noise ratio (MR1.2).

Imaging data acquisition (MR2): The performance of the MRI scanner has been dramatically improved in spatial and temporal resolution (MR2.1), together with much improved tools for image reconstruction (MR2.2), overcoming limitations within the manufacturer's software. In addition a significantly improved procedure has been devised to create high contrast structural images (MR2.3).

Spatial image processing (MR3): The accuracy of MRI is affected by inhomogeneities in the applied magnetic field arising from the different physical properties of bone, air and tissues. A range of techniques has been established, using specialised image acquisitions which measure the magnetic inhomogeneities, in order to compensate for the distortions in images that are otherwise present (MR3.1, MR3.2). Conventional automated image processing can come unstuck when matching images in which there are abnormal regions to a normal brain template. These problems typically arise in the presence of lesions or of artefacts caused by regions of low signal. Matching algorithms have been devised and implemented to compensate for these effects by masking the abnormal regions (MR3.3).

Spatio-temporal modelling (MR4): A range of techniques from the field of pattern recognition has been applied to extend the ways in which the temporal and spatial characteristics of particular brain states can be compared. Methods known as support vector machines (MR4.1) and wavelet analysis (MR4.2) both show some promise as techniques for making these subtle comparisons. As knowledge of brain physiology and function advance, research hypotheses can increasingly be formulated in relation to specific locations or regions of interest (ROIs). Studies of ROIs have the potential for much greater power but have been limited by the lack of analytical tools comparable in scope to those available for whole-brain studies. A significant start has been made in providing a comparable software toolbox for the delineation, visualisation and preliminary analysis of data from ROIs (MR4.3). An improved understanding of the temporal structure of fMRI signals, in particular components of low frequency noise, is being developed. Preliminary studies suggest that there is an association between different parts of the low frequency spectrum and specific brain regions and tissue types (MR4.4).

Clinical applications (MR5): The masked image matching techniques mentioned in MR3.3 have been the basis for validated and automated methods for handling normalisation and registration of functional imaging data and structural images from subjects with lesions or other abnormalities (MR5.1). The use of functional imaging as a tool for the evaluation of neurosurgical candidates has been explored through the use of motor and language tasks that activate characteristic cortical regions in normal subjects (MR5.2). The brains of patients with multiple sclerosis show numbers of small lesions which over time can appear, change size and shape, or disappear. Image analysis methods from the material sciences are being applied to quantify image distortion both locally and globally, with the prospect of being able to derive an objective measure which can be related to the fluctuating clinical severity of symptoms (MR5.3).

Meta-analysis and general statistical methods (MR6): Meta-analysis tools assist in the important task of drawing together the results of several imaging studies to establish commonalities and make comparisons. A non-parametric technique has been established for the meta-analysis of maps showing the peaks of activation (MR6.1). Mappings for converting between various standard brain templates has established, providing a means of collating within a common framework results from published studies in which a variety of different coordinate systems have been used (MR6.2).

Dissemination: Many of the problems that the methods group has dealt with are common to other laboratories doing imaging and behavioural experiments. We have distributed our experience via the imaging and statistics websites, and have made and maintained public releases of our software. In addition, the Outputs section evidences the group's commitment to innovation and leadership in methods research.

Project MR1: Running experiments in the MRI scanner

Scientific Direction: Brett, Cusack, Nimmo-Smith

CBU collaborators: van Casteren, Norris, Cumming, Bor

Research support: Chandler

MR1.1 Various improvements – hardware configuring and standardising – timing – presenting auditory responses.

Running cognitive science experiments in the environment of an MRI scanner is not straightforward, and significant steps have been made to ease the complexity, as well as to increase the range and accuracy of stimulus delivery and response recording.

Experimental timing and scanner synchronisation libraries have been written by Cusack to assist with timing issues in the implementation of visual and auditory experiments. The first provides precise timing beyond the standard Intel/Windows routines using a counter built into the Pentium Chip, which is updated a rate of several MHz. Accuracy was confirmed. The library includes commands to allow critical parts of a program to increase their multitasking priority so they could dominate the system, allowing the presentation of visual and auditory stimuli at precisely specified times. A second library was written to allow precise synchronisation of the MRI scanner, the presentation of stimuli, and the recording of responses. This accuracy of this synchronisation is particularly important for 'event-related' designs, where the haemodynamic response to brief events is modelled. Synchronisation proved problematic because the measured time for the scanner to acquire a functional volume in a time series (repetition time, TR) is not exactly that reported by the scanner software.

For accurate synchronisation it is necessary that the same computer both presents stimuli with high temporal accuracy, and constantly monitors for incoming scanner pulses. This conflict of demands was solved through a novel algorithm. We used the properties of the timing of the concurrent scanner acquisition to reduce the demand to listen for pulses. Although the exact repetition time that will be generated, for any particular set of acquisition parameters, is unknown, the scanner is extremely regular, acquiring at a fixed rate that is microsecond precise, while being within 2% of the nominal TR expected from the scanner. The two clocks can be successfully synchronised on my monitoring just a subset of the scanner pulses. These methods have proven powerful and flexible, and the tools has helped in the implementation of more than 75 experiments at the CBU and elsewhere.

A related problem is the post-hoc recovery of the TR from pulses recorded during the scanning session. A large number of researchers in the CBU and elsewhere use DMDX software for stimulus presentation and response recording. This can be set up to record all responses at specified times during the experiment, including scanner pulses. The timing of these pulses is less accurate than that of the libraries described above, and a relatively small number of TRs may be recorded. Brett and Nimmo-Smith applied the method originally devised by Kendall (1974), to determine the TR from the scanner pulses recorded by DMDX. We have combined this algorithm with parsing of the DMDX output and input files to automate output of stimulus and response times in terms of the TR, as required by analysis software such as SPM.

To present auditory stimuli in the MRI scanner, we have a high quality electrostatic system provided by the MRC Institute of Hearing Research in Nottingham. The software supplied with this allows good control of the timing of stimuli and their level of presentation. However, it was not possible to configure this to receive responses, and van Casteren has written new software which allows greater temporal precision and permits the collection of responses with reaction time measurements.

These software improvements to have been supported by improved and standardised interfaces for configuring the hardware, and recent adaptations to the MRI building have been exploited so that visual stimuli can be directly projected onto a fixed rigid screen, with significantly improved image quality.

MR1.2 Scanner noise cancellation

Scientific direction: Cusack

CBU collaborators: Norris, Cumming, Bor:

There are some neuroimaging experiments where it is desirable to be able to take a verbal response from the subject. One example is in a working memory task where a subject hears a series of numbers and is then cued to repeat them. One problem that arises is recording the responses. While we do have a scanner-compatible microphone, in the resultant recordings it can be hard to hear the subjects' voice above the sound emitted by the scanner, which is above 100 dB SPL in level.

Fortunately, as the source of the sound is vibrations from the gradient coils, which are being driven with great temporal accuracy, the noise made by an acquisition has a fixed form throughout a session. It is therefore possible, by taking a mean over time, to build up any accurate representation of the scanner noise and then subtract this away from the sound file at the appropriate positions. This cancellation procedure is very effective at reducing the scanner noise, reducing it by around 25-30 dB. The sound of the subject's voice is unaffected and becomes clearly audible.The procedure is now routinely available and will contribute to future CBU studies, e.g. Proposal A2.1.

Project MR2: Imaging data acquisition

MR2.1 Echo-planar imaging

Scientific direction: Schwarzbauer

A new echo-planar imaging (EPI) sequence has been developed and implemented on the 3 Tesla Bruker MR scanner at the Wolfson Brain Imaging Centre in Cambridge. It is based on a new software environment called ParaVision Methods Manager (PVM) which allows the design of MR pulse sequences in a strictly modular way. The new EPI sequence was released for public use in April 2002 and has become the standard for fMRI data acquisition in Cambridge. Compared to the previously used Bruker EPI sequence, the new EPI module offers several advantages.

• There has been a 120% increase in temporal resolution, and a whole brain coverage using 21 slices and a matrix size of 64 x 64 pixels with a minimum repetition time of 1.1 s compared with 2.4 s with previous EPI sequences.

• There is a 50 % increase in sensitivity (signal-to-noise-ratio per unit time) as a direct consequence of the increase in temporal resolution, since more data points can be sampled per unit time.

• There is a 25% increase in spatial resolution as now the field-of-view (FOV) can be shifted within the imaging plane which was not possible with the previous EPI sequence. It can therefore be optimally adapted to the size of the subject's head. Consequently, a smaller FOV can be used which typically results in a 25 % increase in spatial in-plane resolution for a given matrix size.

• Finally it is possible to used optimised RF excitation pulses, with slice saturation effects for short repetition times (TR < 2s) being taken into account. The optimum excitation pulse angle (Ernst angle) is calculated and set automatically in order to maximise signal from grey matter regions.

Due to its modular structure, the new EPI sequence provides an excellent starting point for further methodological developments (e.g. compensation for susceptibility induced signal losses, rapid phase mapping, perfusion imaging).

MR2.2 Reconstruction of echo-planar images

Scientific direction: Schwarzbauer

A new software package for the reconstruction of echo-planar images has been developed. This was necessary to overcome some major drawbacks associated with the image reconstruction software provided by the manufacturer. Firstly, it was incompatible with the new EPI sequence. Secondly, it required the scanner control software (ParaVision) to run in the background. ParaVision, however, has only been released for SGI O2 workstations which by current standards exhibit a relatively poor computational performance. Thirdly, it could only be run in an interactive mode which took up a considerable amount of manpower.

The new software package provides a simple and cost-effective solution to the aforementioned problems. It is based on the C programming language and can therefore be implemented on high-performance computers. Data processing is fully automated and requires a minimum amount of human interaction. The user can for example specify a period of time and the program will automatically locate all data acquired during this period. Image reconstruction will then start at a later time specified by the user. This typically happens during the night in order to free computational resources for other applications during regular working hours.

In addition to these economic benefits the new software package has a variety of technical advantages including an improved phase correction algorithm to minimise so-called 'ghosting' artefacts in echo-planar images.

MR2.3 Structural imaging using MDEFT

Scientific direction: Schwarzbauer

The MDEFT (modified driven equilibrium Fourier transform) sequence is known to produce superior results for structural imaging at high field strength in terms of both grey-white matter contrast and signal-to-noise ratio. A MDEFT sequence has been developed and implemented on the 3 Tesla Bruker MR scanner at the Wolfson Brain Imaging Centre (WBIC) in Cambridge. Based on a three-dimensional (3D) data acquisition scheme, whole-brain coverage is possible within approximately 13 minutes at an isotropic spatial resolution of 1mm. Preliminary data acquired in healthy volunteers showed an increase in grey-white matter contrast by 40 % in comparison with the 3D FLASH (fast low angle shot) sequence which has been the standard for high-resolution anatomical imaging at the WBIC. Furthermore, undesired signal from cerebrospinal fluid was suppressed efficiently. Following a final evaluation and testing period, release for public use is planned in October 2002.

Project MR3: Spatial image processing

MR3.1 Using field maps to undistort echo-planar images (with Papadakis)

Scientific direction: Cusack, Brett

MRC-supported student: Osswald

It is inevitable that when a head or body is put in an MRI scanner, the differences in magnetic susceptibilities of bone, air and tissue lead to inhomogeneities in the magnetic field. While some low spatial frequency components of these inhomogeneities can be corrected by shimming, others remain. Some sequences are particularly affected by these inhomogeneities, especially the images from echo-planar sequences usually used for mapping functional activation, which can be distorted and contain areas of dropout. These problems are worse at higher fields, and effects are clearly visible on images from the WBIC 3 Tesla system. We discuss elsewhere current and future plans to deal with dropout (reduction of susceptibility artefacts (MR3.1, Proposal MR1.1); masked normalisation (MR3.3)). Here we describe a system we have implemented to correct for distortion. We measure the actual magnetic field obtained, and then use this to correct for the distortions in echo-planar images (Jezzard & Balaban, 1995).

Acquisition of field maps: With Nikos Papadakis and other members of the WBIC team we developed and tested field-map acquisition sequences. Phase unwrapping: Information in the phase, rather than the magnitude, of MR images can allow us to measure many interesting parameters, such as flow rate or magnetic field strength. Usually, two datasets are acquired, which differ only in the degree to which the phase is influenced by the parameter of interest. One dataset is used as a reference, and subtracted from the phase of the other. In this way, uninteresting phase components that are common to both images, such as the transmitter or receiver characteristics, or those of the digital filtering, are removed. Only the effect of the parameter remains. The phase is usually proportional to the parameter of interest. However, it will have been wrapped into the range [-π, π]. If the parameter we wish to measure gives phase differences that are small enough to fall into this range, then the measured phase can be used directly for parameter estimation. If, on the other hand, the magnitude of the phase difference is large enough to be outside this range, then to recover the true phase, we must restore the missing multiples of 2π. This process is known as phase unwrapping. The phase of voxels in a volume may be unwrapped relative to each other, provided that the underlying phase is relatively slowly changing over space.

Whilst in principle phase unwrapping is simple, in practice it is rather more difficult to implement. The problem is that it is highly sensitive to errors in regions with low signal-to-noise. Localised errors can be propagated into areas with good signal, and lead to a catastrophic failure of the unwrapping process. We designed, implemented and tested a new algorithm for robust 3d phase unwrapping, in which less noisy regions of the phase map are unwrapped first. This algorithm was tested extensively on simulated phase data and on MR field map images, and was found to be robust on both (Cusack & Papadakis, 2002). Collaborations have also been started and grants obtained for the development of new algorithms (MR3.2).

Once the field map has been obtained, it was spatially processed in several ways (masking, expanding, smoothing & rotation). After this, the images need to be accurately coregistered with the echo-planar images to be undistorted. However, this is difficult, as the images are different shapes: the field maps do not contain distortions, but the EPIs do. To solve this, we used a novel method of forward distorting the field maps, so that they are also distorted. The two images are then the same shape, and can be coregistered. Once coregistered, the EPIs can be undistorted using the pixel shift method.

This undistortion system was implemented in C for speed and packaged in an easy-to-use interface written in Matlab using SPM. The overall performance of this procedure has been evaluated in several different ways (Cusack, Brett & Osswald, in press). We found that application of undistortion makes the shape of the functional images more similar to the true shape of the brain and reduces the amount of warping required to transform them to standard space. It also increases the power of group studies by improving overlap of activations across subjects.

This tool is now in widespread use at the CBU (default analysis procedure for all groups, e.g. Proposal A2.4), at the Departments of Psychiatry and Psychology in Cambridge, and at the Centre for Magnetic Resonance Research in Queensland, Australia (default analysis procedure).

MR3.2 Development of new phase unwrapping algorithms (with Huntley and Marklund, Loughborough University)

Scientific direction: Cusack, Schwarzbauer

Grant supported: Marklund

While the algorithm that was described in Cusack & Papadakis (2002) is sufficiently robust to unwrap field maps from normal subjects, there are other phase acquisitions, such as those for encoding blood flow, that are more noisy and do not unwrap correctly. In the field of optics, phase acquisitions are frequently used, and there has been substantial development of robust unwrapping algorithms, and extensions of some optics algorithms to three dimensions offered the possibility of substantially more robust unwrapping. To tackle this line of research, Cusack began a collaboration with Professor John Huntley, who is in the Optics Group at the Wolfson School for Mechanical and Manufacturing Engineering at Loughborough University. We applied for a MRC/EPSRC funded 'Discipline Hopping' grant to employ someone to work on this for one year. A grant of £47,000 was awarded, and Olov Marklund appointed to the post. The new algorithm is based on a 'branch cut' method in which incorrect unwrapping paths are identified and blocked. This algorithm has been implemented and tested, and several papers describing the work are currently in preparation.

An alternative to spatial unwrapping that might be better under some conditions is to acquire many images with different echo times, and calculate the field from the change in phase of a voxel as the echo time changes. We have collected a set of EPI volumes over a range of echo times. Work in optics by Huntley has shown that the optimal acquisition set has a reverse exponential spacing of the parameter that modifies the phase – in this case echo time – and we hope to determine what parameters would be appropriate for the application of this technique to field map acquisition.

MR3.3 Methods and evaluation of voxel-based morphometry (with Good, Ashburner, Friston and Frackowiak, Functional Imaging Laboratory)

Scientific direction: Johnsrude

Before the advent of neuroimaging, brain morphometry (measuring the relative volume of brain areas) could only be accomplished in small-sample post-mortem studies, and, owing to its labour intensive requirements, only in circumscribed regions. In contrast, voxel-based morphometry (VBM) is a whole-brain, unbiased technique for characterising regional cerebral volume and tissue concentration differences in structural magnetic resonance images, and can be used with very large samples. However, voxel-based morphometry is a new technique, and consensus has yet to be reached on how best to implement it. We developed an optimised method of VBM using SPM, and then used this to examine the effects of age on grey matter, white matter and CSF volumes, and the effects of sex and handedness on hemispheric asymmetry, in 465 normal adults (Good et al., 2001a,b). VBM is a methodologically complex procedure, and the method used prior to our work was prone to misregistration from image to image and poor tissue segmentation, both of which could compromise results. The method that we developed involves multiple stages of tissue segmentation, linear and nonlinear spatial normalization, and spatial smoothing, and was designed to optimally register all the images in the sample and give optimal tissue segmentation. Given the complexity of the method, validation of the end result is essential. The evaluations of optimised VBM that we carried out on this large normative sample yielded many observations consistent with previous literature (post-mortem studies), validating it as a morphometric technique. Three considerable advantages of VBM over traditional ex vivo methods are that: (a) much larger groups can be studied so power and sensitivity are likely to be much higher; (b) the brain morphological correlates of individual cognitive differences can be studied; and (c) longitudinal studies are possible. For example, this technique can be used to examine the brain bases of acquired cognitive disorders, or to examine the neural correlates of individual differences in a particular ability (rate of learning to understand systematically distorted speech; see Proposal SL5). The effort that we have made to develop an optimal procedure for VBM opens the door to such studies.

MR3.4 Spatial processing of brain images with lesions and artefacts (with Leff, Rorden and Ashburner)

Scientific direction: Brett

In analyzing brain images, it is usual to transform a scan from an individual to match another individual brain or brain template, a process known as spatial normalization. The normalized brain is easier to compare to data from other brains that have been similarly transformed, and this process is an important step in group analysis for imaging data. The need to compare data across individuals has been the driving force behind much recent research on automated brain matching methods. These methods use mathematical summaries of the differences between two brain images to drive an automated search process looking for the best series of spatial transformations to match the images. These algorithms work well in normal subjects, and have led to an increasing acceptance of standard templates. However, a problem arises when trying to match images with artefacts or lesions; the abnormality contributes to standard measures of mismatch with the template, and the search for the best matching transform is driven to try and match the abnormal signal to some area of the normal template. This can result in severe distortions, and therefore inaccuracy of matching. We have implemented and validated a method to solve this problem, so that images with artefacts or lesions can be matched to standard templates. The method involves manual outlining of the abnormality to create a mask image, which we then use to remove the effect of the lesion on the calculation of image mismatch, and hence on the calculation of the spatial transform. Validation has shown good reproducibility across operators defining the lesion and measurable benefits over previous techniques (Brett, Leff, Rorden & Ashburner, 2001). The method has been included in the standard SPM software for functional imaging analysis. We use this technique to allow us to normalize brains with lesions (see MR15). It has also become part of our standard processing stream in normalizing functional images, which have areas of artefactual signal loss due to magnetic field inhomogeneity (see MR7), it has been used in Progress A1.2 and A5.6, and will be used in Proposals A2.1, A2.4 and A2.5.

Project MR4: Spatio-temporal modelling

MR4.1 Using support vector machines to classify spatial and temporal patterns of brain activation (with Gretton, Mankong, Goh, Hill and Epstein, University of Cambridge)

Scientific direction: Brett, Cusack, Nimmo-Smith

The most common method of analysing MRI data is to focus on temporal patterns in the data. Using the temporal pattern of the stimuli that were presented, we can generate a predicted timecourse from the different events in the experiment and identify voxels for which the predicted timecourse explains variance across scans. This standard approach has several disadvantages:

We cannot use this method when we do not know the timing of assumed neural events - for example where the brain state is not directly stimulus driven, but may fluctuate – as might be the case for stimuli with ambiguous percepts such as the vase-face illusion;

We cannot directly compare the shape and location of activation across brain states;

The predicted timecourse is derived by using an assumed standard haemodynamic response which is common to all events and brain areas. As discussed in MR4.2, this may not be a reasonable assumption.

To tackle these problems, in collaboration with Cambridge University Department of Engineering (Mankong, Gretton, Goh, Hill), we used a tool called support vector machines (SVMs), which are a flexible way of categorising multidimensional data. Given a training set comprising a number of examples of each of two different types of categories, the SVM generates the optimal decision criterion to differentiate the two groups.

In a first project, we used SVMs to model and classify spatial patterns of activation for different stimuli. We took some MRI data from a study in which various kinds of visual stimuli – faces, objects, scenes or houses – were presented in short blocks. To train the SVM, a pair of categories were selected. On each training iteration, the SVM was given a volume of data from a single timepoint in a block of one of the two categories, and a label corresponding to the category. After training, test data were presented. It was found that in most subjects, the SVMs were fairly reliably able to identify the stimulus that was being presented, for all possible pairs.

A second project piloted the use of SVMs to detect brain activation patterns with reduced assumptions as to the shape of the haemodynamic response. We used data from a single fMRI session, during which the subject watched a computer monitor, and responded with a button press to randomly occurring events of 500 ms of a flashing checkerboard stimulus. Standard assumed response analyses identified the visual cortex as responding to the checkerboard stimuli, and a large region in the frontal cortex as not responding to the events. We then trained SVMs to classify the voxels in the visual cortex region as being activated as compared to a series of subsets of the frontal voxels. Each resulting SVM classification function was used to classify all voxels outside the areas used for training. Results showed that the SVM classifier was highly specific to the training areas; for example, the motor cortex, which was identified by the standard analysis, was not classified as active by the SVM. This suggests that the time course of the visual region is distinct to the region itself.

Future applications of SVM to fMRI studies, e.g. Proposal A1.2, could help identify similarities and dissimilarities between patterns of brain activation.

MR4.2 Applications of wavelet analysis

MR4.2.1 Spatial processing for signal detection in functional images (with Turkheimer, Aston and Cunningham, MRC Cyclotron Unit, London)

Scientific direction: Brett

Standard statistical analysis approaches to functional imaging data involve three steps; the images are first smoothed spatially to increase signal to noise at the resolution of usual brain activations, which tend to extend across many brain voxels. The second step is time series analysis of each voxel to generate a map of some parameter relating the statistical model to the time series at each voxel. Last, a multiple correction procedure may be required to allow for the number of voxels analyzed, and which must take into account the smoothness (spatial correlation) of the voxels. One problem with this approach is that we often do not know what shape an activation will be; the matched filter theorem implies that activation is best detected when the smoothing filter is the same size and shape as the activation. Thus, it can be difficult to choose the correct smoothing for the analysis.

Wavelets may offer a useful method of spatial analysis. Wavelet decomposition breaks down an image into a series of coefficients, reflecting the presence at a particular location of a pattern, defined by the wavelet used. The decomposition proceeds in levels, so that the wavelet coefficients reflect the presence of the wavelet pattern at larger scales as the levels increase. The coefficients at different levels are therefore analogous to signal at different levels of spatial smoothing.

We have used wavelets for spatial analysis, by taking the pre-processed images ready for statistical analysis, and replacing each image with the decomposition of the image into wavelet coefficients. We then regress the standard statistical model against the time series of wavelet coefficients, instead of the voxel values, as would be the case for a standard analysis. The analysis results in statistical maps; each statistic refers to a particular wavelet location, instead of a voxel, as would be the case for a standard analysis. This has major advantages; there are many well-described methods for removing noise from such maps, and the value for each wavelet location and level is approximately independent of that for any other location and level, so that we can use simple correction procedures to detect significant signal. By analysing across all wavelet levels, we can look for signal of many different sizes simultaneously, thus avoiding the problem of choosing a smoothing kernel. We have shown that this approach offers a powerful method of estimating signal in PET images (Turkheimer et al., 2001), and have implemented the algorithms in a toolbox for use with SPM software (see MR21 in this progress report).

MR4.2.2 Wavelet analysis for characterising time series noise in fMRI (with Fadili and Bullmore)

Scientific direction: Brett

Wavelets are also proving useful in the analysis of fMRI time series. fMRI noise has a distinctive pattern, with increasing noise at lower frequencies. Wavelet analysis offers a useful method of characterising such noise at different brain locations (Fadili, Bullmore & Brett, 2000).

MR4.3 Region of interest analysis of functional imaging data (with Anton, Valabregue and Poline)

Scientific direction: Brett

Most functional imaging studies use analyses that look for effects anywhere in the brain. The standard approach is to calculate a statistic relating the experimental effect of interest to the data for each brain voxel. This method has the advantage that it can detect strong effects without a priori constraint on the area that activation will occur. Problems arise when we wish to ask the question whether a particular brain area has been activated; voxel by voxel approaches have low power, because of the need to correct for multiple comparisons across voxels, and because the smoothing kernel chose may not be correct for the area of interest.

The most direct answer to the question "has this area been activated" is to use a region of interest (ROI) analysis. Here we define a region, and perform the statistical test on the summary time course of the voxels within the region. This approach has several advantages. We increase power greatly by avoiding the multiple comparison problem. By specifying the shape and size of the region, we avoid the problems of having to choose the correct spatial smoothing. Because the analysis is simpler in principle than analysis of multiple time-series simultaneously, it is easier to use standard techniques for data diagnosis and model selection. Lastly, the results from an ROI analysis are often simpler to interpret than those from a whole brain analysis.

Although ROI analysis has been used very successfully in functional imaging -- e.g (Kanwisher et al., 1997), it is not generally used. This is reflects the fact that there has been very little development in ROI software for statistical analysis. We have implemented a toolbox for ROI analysis to work with SPM software which allows the user to specify, import, draw and combine ROIs, extract time course data and run and review statistical analyses. As well as providing a platform for further theoretical development (see below), we have used the toolbox as a method of popularising the use of ROI analyses in the functional imaging community.

MR4.4 Regional characteristics in the frequency analysis of tissue types in resting fMRI data

Scientific direction: Brett, Schwarzbauer

Grant supported: Andrade (Marie Curie Fellow)

Studies of FMRI signal have shown that typical time courses show an increase in noise at lower frequencies, in a pattern that is known as 1/f. The sources of this noise are not well understood; although low frequency noise has been attributed to physiological artefacts, such as aliased heartbeat or respiration cycles, similar noise distributions have been seen in cadaver brains and MRI phantoms (Zarahn et al., 1997; Smith et al., 1999). It is clear that some low frequency fluctuations are of physiological interest, as low frequency drifts in signal correlate between connected areas, such as left and right motor cortex, even in resting state data, when subjects are performing no movements and no task (Biswal, Yetkin, Haughton & Hyde, 1995). Andrade was awarded a Marie Curie fellowship to look at regional differences in FMRI noise, and has studied low frequency power and correlation in resting state and activation datasets. Using structural images and the undistortion tools described in MR3.1, the EPI images were segmented into in white matter, gray matter and CSF. Analyses showed that there was a concentration of low frequency noise in the frontopolar brain regions, whereas medium frequency noise was most marked in visual, motor and parietal cortex. There was a distinctive peak in medium-range frequencies in ventricular CSF which was consistent with aliasing from respiration. These regional effects were consistent across scanning runs and individuals Previous studies of resting state correlations between brain areas have not investigated the frequency spectra or consistency of these effects across areas and individuals. This may be of interest because the nature of these effects are not well understood (Obrig et al 2000), and the distribution of frequency spectra may reveal clues as to their physiological basis. We have developed software and display methods to look at coherence (which can be thoughts of as correlation at a particular frequency) in pilot datasets to determine the nature of these connectivity correlations. We intend to investigate these phenomena with further experiments (see Proposal MR2.3).

Project MR5: Clinical applications

MR5.1 Spatial processing of brain images with lesions (with Leff, Rorden and Ashburner)

Scientific direction: Brett

Research on patients frequently involves brain imaging; structural scans show the location of the lesion, and functional imaging can give information on brain recovery and reorganisation. It is often useful to be able to match the brain of a patient with those from other patients or normal controls. In functional imaging, this is achieved using automated image matching methods; however, these are disturbed by the presence of the abnormal signal from the lesion. As described in MR3.3, we have implemented and validated a method of dealing with this problem, so we can use automated matching algorithms on lesioned brains (Brett, Leff, Rorden & Ashburner, 2001). This has allowed a standard format for comparison and display of brain lesions (Rorden & Brett 2001) and allows comparison of lesion site with other data - such as that from functional imaging. It has become standard procedure for processing of structural images for patients from the patient panel.

MR5.2 Application of fMRI to the evaluation of neurosurgical candidates.

Scientific direction: Johnsrude

Quality of life and life expectancy of patients with focal brain diseases such as tumours or epilepsy can be dramatically increased by surgical resection of affected tissue. In such cases, the goal is to remove as much damaged or diseased tissue as possible, while at the same time sparing essential functions, such as language and motor abilities, as much as possible. The advent of neuroimaging has provided a way for the organization of such functions to be assessed noninvasively prior to surgery, providing surgeons with the locations of eloquent cortices in individual patients. We developed a battery of functional magnetic resonance imaging tasks that identify motor, motor planning and language function on a clinically realistic timescale, which have evaluated in 11 healthy volunteers for comparison with patients with brain lesions.

Primary motor function was tested using a 15-min task assessing right and left-handed finger and toe opposition compared to a rest condition. The influence of rate of opposition was assessed by including alternating blocks of 1Hz and 2Hz, cued by tone pips delivered through headphones. Motor planning function was assessed using a 5-min, 4-choice motor reaction task in which the volunteer responded to blocks of cued and uncued tasks using a joystick, interspersed with a rest condition. Language function was assessed using a 16-min task involving word repetition ("repeat") and verb generation ("generate") tasks alternated with rest conditions.

Results in our right-handed normal volunteers were in agreement with existing literature. The motor task identified primary motor somatotopy to a highly significant extent within subjects. These results were consistent across subjects. An increased level of activation in primary motor cortex and auditory cortex was observed when results at 2Hz were compared to those at 1Hz, across subjects. The motor reaction task recruited cortical regions associated with motor planning in agreement with previous studies. Such areas include primary sensorimotor cortices, supplementary motor area, anterior cingulate and cerebellum bilaterally. The language task (using the ("generate" - "repeat") contrast) revealed significant recruitment of left inferior frontal cortex in all, which is likely to be indicative of left-hemisphere dominance for language in these right-handed volunteers. These results for all three tasks were both highly consistent across subjects and in agreement with known brain organization and previous literature.

This protocol is now being used as part of the evaluation of selected neurosurgical candidates prior to surgery, and the surgeons find the information it provides to be helpful in tailoring their surgical interventions. Research to establish the utility of this examination in surgical intervention and outcome is ongoing.

MR5.3 Tracking of brain distortions in multiple sclerosis (with Grantham and Goldrein, Cavendish Laboratory, Cambridge; Sjödahl, Division of Experimental Mechanics, Luleå University of Technology, Sweden)

Scientific direction: Cusack, Johnsrude

Multiple sclerosis (MS) is one of the most common diseases of the nervous system. It usually causes sudden neurological symptoms including vision loss, paralysis, numbness, and walking difficulties. MRI is an important tool for diagnosis. In MRI scans of the brains of people suffering MS, small lesions can be seen to appear and disappear over time. However, the number of lesions does not correlate well with the severity of the problems that a person will experience. One reason for this is that some lesions may disrupt less important, or more robust, areas of the brain. Another reason might be that the effect of the lesions depends on the extent to which they distort the surrounding tissue.

The aim of this collaborative project was to use techniques that were developed for measuring deformations in solids under very high stress (e.g., concrete or perspex under impact from projectiles) to measure distortions in the brain due to MS. The basis of the procedure is to take a small subsection of one image, and correlate it at various displacements with another image. The procedure, which currently uses two-dimensional slices, has been highly optimised, and can measure distortions of a fraction of a voxel. By applying known distortions to brain images, we were able to validate that the technique works. We have then applied it to longitudinal data obtained from the Montreal Neurological Institute and used it to visualise the distortions as a result of the lesions. We hope to quantify the degree of distortion overall, and at various points in the brain, and then correlate these measurements with clinical data on the severity of symptoms over time. We are currently preparing a paper to describe the technique and the evaluations. Mikael Sjödahl has applied for a grant from the Swedish Research Council to continue this work.

Project MR6: Meta-analysis and general statistical methods

MR6.1 Meta-analysis of brain imaging studies

Scientific direction: Nimmo-Smith

The typical neuroimaging study identifies a number of regions of the brain which are activated by a specified mental task. It is important to be able to compare the regional distributions identified by different studies to see if the foci have different extents.

There appears at present to be no established way of directly comparing two single studies. However, when we superimpose the activation maps of a number of different studies which involve similar mental functions then some consistencies may appear to the eye. Moreover when we combine another group of studies a seemingly different combined map may appear.

Objective statistical methods are needed to confirm these subjective impressions. Nimmo-Smith & Duncan (2001) a non-parametric method which generalises the classical non-parametric Kolmogorov-Smirnov two-sample test to the three-dimensional distributions of regional activation. There were a number of novel features to the algorithm by which this statistical test was implemented, to meet the need for an efficient means of locating the maximum of a combinatorially defined function in a lattice with, for typically encountered datatsets, a very large number of nodes.

We demonstrated the sensitivity of this new test by applying it to two sets of data. The first was assembled from 20 published studies manipulating 5 different aspects of working memory and perceptual demand. The second dataset was combined from 14 functional imaging studies investigating retrieval from episodic memory. The test allows us to conclude that, while there is some overlap in the regions that activated by working memory and retrieval from episodic memory, there are systematic differences in the two patterns of regions, in particular the presence of a consistent distribution of frontal activation in working memory tasks.

By contrast, when the same test is applied to the comparison of regional activations for each pair of the 5 aspects of working memory no significant differences were identified in the regional distributions.

This meta-analysis technique was initially developed for Duncan & Owen (2000), and has subsequently been successfully applied to questions concerning frontal asymmetry in positive and negative emotion (Lawrence & Murphy, 2001) and the comparison of frontal activation of schizophrenics with that of normal subjects (Hill, Mann, Stephenson, Laws & McKenna, 2002). Two papers are in preparation, one intended for the neuroimaging community describing the method and its application, the second detailing the novel technical aspects of the algorithm. Software written in C++ with a Matlab interface is being prepared for distribution.

MR6.2 Converting between standard brain templates (with Christoff and Lancaster)

Scientific direction: Brett, Cusack

The final stage of the analysis of functional imaging data is to label the detected area of activation (Brett, Johnsrude & Owen, 2002). Labels may be in terms of anatomical structure, such as a named gyrus, or, more commonly, a stereotaxic co-ordinate in terms of a standard brain, or an estimated Brodmann's area. The atlas of Talairach and Tournoux (1988) has become a standard in the field.

The usual method of functional imaging analysis involves matching the brain image of each subject to an image of a standard brain or template; in recent years the standard templates have become those from the Montreal Neurological Institute (MNI).

Problems can arise because the MNI templates do not exactly correspond to the Talairach atlas (Brett, Johnsrude & Owen, 2002), although the differences are not always allowed for in reporting activation labels. It can therefore be difficult to compare co-ordinates from studies which have matched directly to the Talairach atlas, and those that have used the MNI templates; this difference can bias the results of meta-analyses, and lead to inaccurate estimation of Brodmann's areas as determined from the Talairach atlas.

We have implemented a simple estimated transform that can convert co-ordinates between MNI and Talairach brains. This transform has been used in published meta-analyses (Duncan & Owen, 2000; Lawrence & Murphy, 2001), and has become standard in third party software (see Talairach Space Utility, mri3dx, and MRIcro in References). We are also extending this work by developing more sophisticated matching transforms (Brett, Christoff, Cusack & Lancaster, 2001).

Dissemination

Teaching fMRI methods

Scientific direction: Brett, Cusack, Nimmo-Smith, Schwarzbauer

Functional imaging is a new technique, and the data present many technical and theoretical complexities. As a group we have set a high priority on teaching the methods of fMRI data acquisition and analysis to the Cambridge imaging community, and beyond. Teaching has taken the form of contribution to formal imaging courses, regular talks at the weekly imaging methods group, and the construction of a comprehensive web site, which has become one of the main tutorial web sites for functional imaging worldwide. Brett has been an invited speaker at imaging courses in Paris, has delivered a 3-day course on functional imaging using SPM software in Melbourne, Australia. He is the first author of a tutorial chapter on multiple comparison correction methods in functional imaging in the forthcoming second edition of a major textbook on functional imaging (Frackowiak et al., 1998).

Teaching statistical research methods

Scientific direction: Nimmo-Smith, Watson

During the review period there has been a significant increase in the numbers of research students attached to the Unit, and also a more structured approach to providing these students with a good grounding in research methods. The statistics group has contributed to this by running courses in Summer 2000 and Autumn 2001. Lecture notes are available on the Unit's statistics website. It is planned to make this an annual fixture, with the content of the course being reviewed to ensure maximum relevance. A statistics website is being developed to provide information and guidance on a wide range of statistical issues.

Software development and distribution

Scientific direction: Brett, Cusack, Nimmo-Smith, Schwarzbauer

Our work has involved the development of software implementing algorithms, or solving other problems in functional imaging analysis. We have assumed a policy of distributing our software freely to the wider imaging community, usually under the GNU software licence (wwww.gnu.org/copyleft). This allows other scientists to replicate our work, increases the visibility of the CBU in the imaging community, motivates clear programming style, and provides feedback on potential improvements that are useful to our own work. Brett has also contributed to SPM, the most commonly used analysis package for functional imaging. Software released and used elsewhere in Cambridge or external laboratories are (users in brackets):

Timing and scanner synchronisation routines (Experimental Psychology, CSL, Psychiatry, Lyon)

These tools were wrapped up into ActiveX libraries to allow access from any Windows programming language – most commonly Visual Basic. They are in widespread use for scanning at the WBIC, both within the CBU (all groups) and elsewhere (Departments of Psychology, Psychiatry). It has also been used for experiments running at FMRIB in Oxford and in Lyon, France. The design of the scanner synchronisation tool has proved flexible, and many different types of experiment have been written, including regular block designs, regular event-related designs, irregular event-related designs with a randomised inter-trial interval, and response-paced designs.

Bruker image conversion program (Experimental psychology, WBIC, CSL, Marseille, Brisbane)

The Bruker scanner stores raw and reconstructed data in a proprietary format. There has been no standard software for conversion of Bruker images to Analyze format, required by SPM. In the Bruker format, the orientation of the reconstructed voxels is encoded in a complex way in several text file headers. In consultation with Bruker, we decoded the various parameters and implemented a command line conversion utility that will output the reconstructed images and orientation information in a format understood by SPM. Images in a session are thus automatically coregistered, which eases subsequent preprocessing, and reduces orientation errors.

Undistortion toolbox (Experimental psychology, WBIC, CSL, Brisbane)

The algorithms described above have been implemented in C and Matlab, and packaged into a toolbox that will run within SPM.

Phiwave wavelet toolbox for SPM (MRC Cyclotron Unit / Imaging Research Solutions Ltd)

The wavelet processing routines were integrated with SPM99 software, so that we could use the statistical machinery of SPM to define and estimate statistical models; the wavelet routines are thus transparent to the user, and they have full access to a wide range of statistical models.

DMDX utilities for FMRI (University College, London)

DMDX software is widely used for fMRI experiments because of its flexible macros for experimental design and accurate timing. These perl programs and libraries parse data from DMDX input and output files, calculate the TR from recorded scanner pulses (MR1.1), and output stimulus and response times in terms of the TR, as required for analysis in software such as SPM.

ROI toolbox for SPM (Experimental psychology; WBIC, CSL, Marseille, Paris, Penn)

We wrote and tested routines for defining, storing, converting and combining ROIs; Statistical routines were rewritten from SPM to use data from ROIs instead of voxels; the SPM model format was adapted to deal with ROI data. The software works as toolbox within SPM, and will import previous SPM models and planned comparisons, build and display ROIs from SPM activations, images and arbitrary shapes, read data within the ROI from images, and output data for further analysis or input into a statistical model.

Render_cols meta-analysis co-ordinate display routine (Stanford, CU Psychiatry)

This routine, based on SPM96, accepts as input a text file specifying points to mark on the surface of a rendered brain, and displays these in a range of colours. This has proved particularly useful for displaying activations for similar tasks across many studies (Duncan & Owen 2001, Lawrence & Murphy 2001).

Meta-analysis of distributions of peak activation (CU Psychiatry)

Software for applying the three-dimensional Kolmogorov-Smirnov analysis described above (MR18) was developed in Matlab with special purpose code written in C for the efficient handling of the binary tree structures which allow datasets of a realistic size to be analysed in an acceptable length of time.

Display_slices image display software (widespread use)

These routines extend the display options in SPM, by offering a wide range of options for displaying multiple activation maps on any set of arbitrary slices through an image.

Scanner noise cancellation tool (Psychiatry)

The tool was developed in Visual Basic, and requires minimal input from the user – just the approximate TR. It then determines the precise TR, forms the mean and does the cancellation. It is currently being applied to a working memory study.

Batch SPM programming for PET studies (widespread use)

The standard SPM interface can require a lengthy dialogue describing the design and the data files. Not only can this be a time-consuming and error-prone process, but the procedure needs to be repeated if even small changes (e.g. adding or dropping a covariate) are made to the statistical model that is being fitted. A modified version of the distributed version allows for all the steps to be specified in advance in a text file which can be easily changed using any text editor. The batch file can be used for keeping track of the datasets, designs and analyses, and for model selection.

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EXTERNAL GRANTS

Awarded Oct 2000, commenced Sept 2001: MRC Discipline Hopping Grant (£47,000) "Development of noise-immune three-dimensional phase unwrapping algorithm for fMRI analysis". The grant was awarded jointly to Prof. J. Huntley (University of Loughborough) and Rhodri Cusack. A candidate from Sweden, Olov Marklund, was chosen at interview and commenced work in Sept 2001.

Awarded June 2002: EPSRC call - Metrology for Life Sciences (£210,000) "Angiography and magnetic field mapping of the brain using phase-contrast MRI and robust 3-D phase unwrapping." Applicants: Prof Jon Huntley (Dept Mechanical Engineering, University of Loughborough), Rhodri Cusack and Christian Schwarzbauer.

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