Neuromagnetic correlates of memory and spoken language processing as biomarkers of incipient dementia

Lisa Michelle Brindley

Clare Hall

September 2011

This thesis is submitted for the award of Doctor of Philosophy

Statement of length

This thesis does not exceed 60,000 words in length (excluding bibliography, figures and appendices) in accordance with the limits set by the Biology degree committee of the University of Cambridge for the award of PhD.

Preface

This dissertation is the result of my own work and includes nothing which is the outcome of work done in collaboration except where specifically stated in the text.

I would like to thank and acknowledge the following:

Elekta AB (Sweden), Elekta Neuromag Oy (Finland) and the Medical Research Council (UK) for providing the funding to make this work possible.

My supervisors Yury Shtyrov and Rik Henson, who took primary responsibility for supervising the passive linguistic and active memory paradigms respectively, for teaching me how to do science in their different ways and generally being good guys. Also for all that reading and commenting upon chapters, detailed and insightful feedback, and email discussions that made me think.

Rachel Holland who conducted the stimulus validation for the passive paradigm and collected the younger group data described in chapter 6, as well as a proportion of the older group data described in chapter 7. Friedemann Pulvermüller, Kambiz Tavabi and Karalyn Patterson for many discussions pertaining to those data.

MEG operators Clare Dine, Maarten van Casteren and Oleg Korzyukov for their assistance with MEG data collection and many varied chats whilst doing so.

Peter Nestor for inviting patients to participate in the study and providing his 'best guess' diagnoses for the memory clinic group. Kate Dawson and Tina Emery for collating and making available patients' and controls' neuropsychological test scores respectively.

John Olichney for providing his original active memory paradigm stimuli, his useful comments upon the MEG/EEG comparison in chapter 2 and taking time out of his trip to the UK to come and visit us in Cambridge.

Jason Taylor for sharing his expertise regarding the active memory paradigm and analysis of sensor SPMs, and Peter Watson for his useful advice upon several statistical analyses.

All those above and many other colleagues, for making the CBU a great place to be; especially my office mates Zubaida Shebani and Raliza Stoyanova, who shared stories, laughter, healthy snacks and a few tears on the PhD rollercoaster.

My parents, Linda Balzanella and Michael Brindley, my brother Mike, and their partners; for your love and support, for always encouraging the belief that I can achieve whatever I set out to do and each showing great strength and determination in your own lives.

Finally – Leo! The most 'ownage' son ever, for accompanying me throughout this journey and making me laugh. For your faith in me, kindness and funniness, for sharing exciting adventures, making me very proud and reminding me what life is really about!

Neuromagnetic correlates of memory and spoken language processing as biomarkers of incipient dementia

Lisa Michelle Brindley

This thesis examines the utility of two magnetoencephalopgraphy (MEG) paradigms in providing biomarkers for incipient Alzheimer's-type dementia. The 'active memory' paradigm crosses factors of congruency and repetition and has shown ability in electroencephalography (EEG) to discriminate mild cognitive impairment (MCI) patients who subsequently converted to probable Alzheimer's disease (pAD) from those who did not. The 'passive linguistic' paradigm is a novel modified oddball paradigm that probes modulation of pre-attentive auditory responses by psycho-linguistic variables.

MEG effects were characterised in young controls in sensor space, before spatio-temporal regions of interest (ROIs) were identified in older controls age-matched to patient groups. Comparisons between older controls and patients with pAD were used to establish which effects/ROIs were sensitive to pAD. Classification models were constructed using logistic regression and a 10^{th} percentile thresholding method. Finally, we turned to a group of patients referred from a memory clinic whose diagnoses were ambiguous; some were experiencing incipient dementia (MCI) whilst others' memory symptoms were due to non-organic causes. Receiver operating characteristic (ROC) curves and logistic regression were used to assess if MEG measures significantly predicted provisional diagnosis and particularly whether they improved diagnostic accuracy beyond that offered by neuropsychological testing. As definitive diagnoses were not available at the time of writing, our MEG measures were compared against the provisional classifications of an experienced consultant neurologist.

Several measures in both paradigms were sensitive to pAD and many were related to neuropsychological measures of memory and/or language. The active paradigm 'congruent repetition effect' predictor improved upon MCI classification accuracy obtained from neuropsychology alone. Passive paradigm predictors, most notably a measure of morpho-syntactic processing conflict, increased sensitivity to MCI; however unequal sub-group sizes meant that improvements in accuracy did not reach significance. Longitudinal follow-up is planned to obtain definite diagnoses against which MEG measures will be evaluated.

Contents

Chapter 1 - Introduction

Prevalence of dementia increases with age, such that one third of individuals aged 80 or over are likely to develop it (Ritchie & Lovestone, 2002); with rising life expectancy, dementia is a burgeoning problem for society as well as individual suffers and their loved ones. Given limited ability to identify those at very early stages of dementia and thus offer treatment during the optimal time window, this thesis aims to explore the potential utility of magnetoencephalography (MEG), a neurophysiological brain imaging tool with high temporal and spatial sensitivity, to produce correlates of cognitive processes that could serve as biomarkers capable of enhancing diagnosis of incipient Alzheimer's disease. In this chapter, the features of Alzheimer's disease (AD) are described, as are those of mild cognitive impairment (MCI), a high risk state for development of dementia. Subsequently, the neurophysiological bases, instrumentation and interpretation of MEG signals are described, followed by an overview of previous research pertinent to the cognitive paradigms that are employed in the current investigation: 1) an active memory paradigm, which draws on work exploring semantic and episodic memory, and 2) a modified passive oddball paradigm that assesses pre-attentive responses to spoken language stimuli.

1.1 Diagnosis of incipient dementia

This section contains an overview of the features of Alzheimer's disease, extant means of identifying those at high risk of developing dementia and the concept of mild cognitive impairment. A test battery used to detect impaired cognitive functioning in individuals who present with memory complaints is briefly described and the suitability of magnetoencephalography (MEG) as an assistive diagnostic tool is discussed.

1.1.1 Alzheimer's disease

Alzheimer's disease (AD) is the most common type of dementia. Symptomatically, AD is characterised by gradual cognitive decline, typically with initial loss of episodic memory for recent events that progresses along a retrograde trajectory, eventually leading to severe amnestic impairment and decline in multiple cognitive domains, including attention and language (Adlam, Bozeat, Arnold, Watson, & Hodges, 2006; Dudas, Clague, Thompson, Graham, & Hodges, 2005; Mathuranath, Nestor, Berrios, Rakowicz, & Hodges, 2000; Mioshi, Dawson, Mitchell, Arnold, & Hodges, 2006; Perry & Hodges,

1999; Perry, Watson, & Hodges, 2000). At early stages it impairs daily activities, before progressing to total incapacity, ultimately resulting in death.

Pathologically, AD involves loss of cortical (initially entorhinal and hippocampal) neurons and synapses, associated with deposition of amyloid plaques and neurofibrillary tangles (Terry, et al., 1991). As these depositions, a characteristic feature of neurodegeneration, can only be conclusively identified post-mortem, individuals fitting the clinical picture of AD are referred to as having dementia of Alzheimer's type (DAT) or probable Alzheimer's disease (pAD). Pathology becomes more widespread as the disease progresses, increasingly encroaching upon temporal lobe structures and sensory association cortices (H. Braak & Braak, 1991). Although the pattern of neocortical spread is variable, there is relative sparing of primary sensory areas (E. Braak, et al., 1999). In addition to cortical degeneration, AD is associated with a loss of sub-cortical neurons resulting in disruption to both adrenergic and cholinergic neurotransmitter systems (Friedman, Adler, & Davis, 1999; Schliebs & Arendt, 2006), with functional consequences for learning and attentional processes. The most common therapies for pAD are acetyl-cholinesterase (ACE) inhibitors, which reduce the break-down of acetylcholine in the synaptic cleft, increasing the amount available to stimulate post-synaptic receptors. These treatments act to slow the rate of cognitive decline and improve behaviour and activities of daily living but are only effective for a period of up to 3 years, and most beneficial when administered early in the course of the disease (Giacobini, 2001). Given the concept that pathological load begins to accumulate long before clinical symptoms are experienced (E. Braak, et al., 1999), with frank deficits in cognitive function emerging much later (see *Figure 1.1*), and that when a threshold level is reached, cognitive symptoms progress more rapidly from subtle impairments to obvious manifest symptoms of dementia (Nestor, Scheltens, & Hodges, 2004), there is a strong argument for identifying individuals in this early 'pre-dementia' phase so that treatment may be administered at the timeliest opportunity.

1.1.2 Mild cognitive impairment (MCI)

Mild cognitive impairment (MCI) is defined as a 'high risk' state for development of dementia, in some cases prodromal to AD, where some cognitive deficits are evident but not sufficiently severe to justify a diagnosis of dementia. MCI falls into amnestic (aMCI, with impaired memory performance), and non-amnestic (naMCI) sub-types, within each of which single or multiple cognitive domains may show a deficit relative to age-matched

norms. Those classified as aMCI are likely to be experiencing incipient AD and incidence of progression to pAD varies from 6-15% per year (depending on criteria used for MCI classification), compared to base rates of 1-2% in the general population (Petersen & Negash, 2008; Petersen, et al., 2009). Conversion rates are higher for multi- than single-domain aMCI (Mitchell, Arnold, Dawson, Nestor, & Hodges, 2009), and indeed, pure amnestic MCI is reported to be rare, with additional attention and/or semantic impairments most often identified (Alladi, Arnold, Mitchell, Nestor, & Hodges, 2006; Dudas, Clague, et al., 2005; Perry, et al., 2000). A post-mortem study found that the neuropathological load in patients classified as aMCI when they died was overall intermediate to that found in normal ageing and in patients with a diagnosis of pAD (Petersen, et al., 2006).

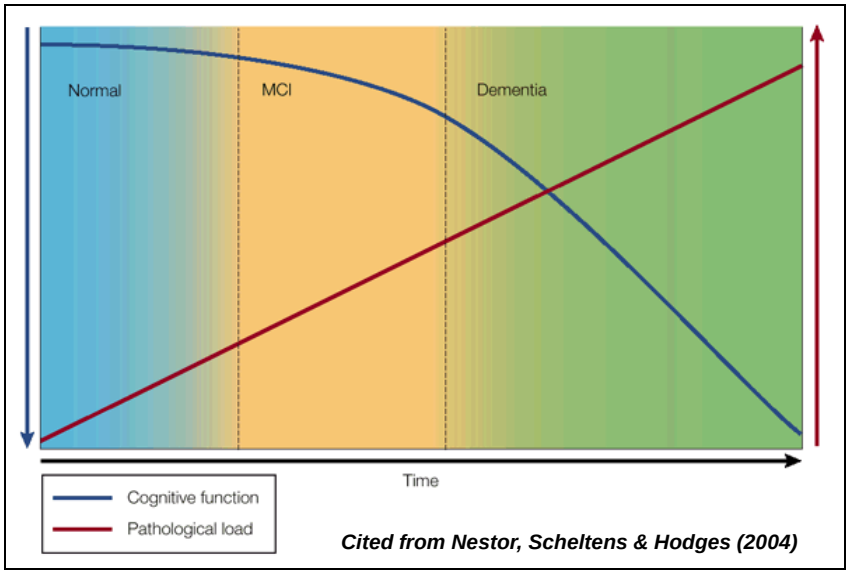


Figure 1.1: Pathological load and cognitive function in incipient dementia

It is the case that memory gradually declines in later life, although this is mostly attributable to changes in fronto-striatal pathways, distinct from the medial temporal lobe atrophic changes characteristic of AD onset (Hedden & Gabrieli, 2004). Inter-individual variability in cognitive performance also increases beyond around 60 years of age, with some elderly individuals performing at the same level as young adults whilst others decline more steeply. These factors make MCI even more difficult to behaviourally distinguish from 'normal' ageing, which is why effects of ageing are another topic of this thesis. In addition to the role of environmental factors and genetic predispositions affecting extent of structural changes with age, high-performing individuals have been suggested to have greater cognitive reserve; that is they are better able to strategically

compensate for structural changes (Buckner, 2004). Some functional imaging correlates of cognitive reserve have been identified in healthy older individuals: subtle differences have been reported in fMRI (functional magnetic resonance imaging) studies that suggested reduced asymmetry in older relative to young adults during verbal encoding (Cabeza, 2002) and reduced posterior and increased frontal activation (Davis, Dennis, Daselaar, Fleck, & Cabeza, 2008). That higher-performing older individuals tend to show these increases in bilateral/frontal activity, whereas low-performing individuals do not (Buckner, 2004; Cabeza, Anderson, Locantore, & McIntosh, 2002; Reuter-Lorenz & Cappell, 2008), may represent a strategic compensation mechanism, whereby individuals with greater cognitive reserve are able to recruit additional brain areas to successfully perform tasks. An individual's cognitive reserve (which may be indicated by pre-morbid IQ) will affect when cognitive decline becomes apparent (Corral, Rodriguez, Amenedo, Sanchez, & Diaz, 2006). Those with greater reserve may carry a far greater pathological load before symptoms emerge and criteria for cognitive impairment are met, maintaining functioning and quality of life for longer, but also potentially delaying diagnosis.

The heterogeneous group of individuals who present at a memory clinic but do not fit the cognitive profile for neurodegenerative disease, MCI or another 'organic' disorder such as vascular dementia, are often referred to as 'worried well' (WW). These may comprise those noticing typical effects of age upon memory ability but fear something more sinister, as well as individuals suffering more affective disorders such as depression that are associated with transient impairment of memory function (although note that depression is co-morbid in around 10% of pAD cases, Steffens & Potter, 2008), or occasionally those expressing very mild cognitive symptoms who may later develop MCI. Thus it is important to distinguish the WW from those with MCI. Indeed, even a diagnosis of aMCI does not indicate inevitable progression to pAD, so there is a need to develop biomarkers that may predict with greater accuracy who will go on to develop dementia and who will stabilise, in order to define the optimal available treatment at the earliest possible stage.

1.1.3 Neuropsychological tools in dementia diagnosis

Different methods are used to identify aMCI. Some require a clinical history of progressive memory decline, coupled with normal performance upon a gross cognitive screening tool (e.g. a score of >23/30 on the mini mental state exam, MMSE), whilst others use a strict threshold (e.g. >1.5SD below mean for age) for the memory

components on a battery of standard neuropsychological tests (Nestor, et al., 2004; Petersen, et al., 2009). Additionally, activities of daily living must be unaffected and clinical rating criteria for dementia proper must not be met. Notably, any behavioural test is susceptible to strategic effects; as noted above, those with greater cognitive reserve may successfully compensate for structural or physiological deficits and perform within expected 'normal' limits for their age.

We focus here on studies employing an established neuropsychological cognitive test battery used for dementia screening and monitoring, the revised Addenbrookes Cognitive Examination (ACE-R), which was completed by all patients who participated in this study and also by a sub-set of older controls. The ACE-R has been validated for diagnostic and monitoring purposes within several patient groups (Davies, Dawson, Mioshi, Erzinclioglu, & Hodges, 2008; Mioshi, et al., 2006) and is comprised of multiple sub-components examining memory, attention/orientation, language, verbal fluency and visuo-spatial abilities. Total ACE-R scores above a threshold of 88/100 have a good prognosis (Mitchell, et al., 2009) and have discriminated healthy controls and MCI with sensitivity of 94% and specificity of 89% (Mioshi, et al., 2006). Furthermore, a higher ratio of performance on verbal fluency and language relative to memory and orientation sub-components (VLOM ratio) discriminates early stages of AD from fronto-temporal dementia (Mathuranath, et al., 2000; Mioshi, et al., 2006). Finally, a total ACE-R score of 88 or above but low sub-component scores restricted to memory and (phonological) verbal fluency domains was found to be strongly related to cognitive symptoms resulting from purely affective disorders rather than incipient dementia in individuals with subjective memory complaints (Dudas, Berrios, & Hodges, 2005).

1.1.4 Neuroimaging tools in dementia research and diagnosis

Whilst MCI is not a formal diagnostic entity but rather a construct that characterises a state of cognitive impairment, development of physiologically-based markers that are not confounded by strategic effects might aid earlier and more reliable identification of incipient dementia, enabling interventions to be undertaken at an optimal time. Studies of brain structure in pAD, particularly with magnetic resonance imaging (MRI) have consistently found medial temporal lobe (MTL) atrophy, however these studies used patients already at moderate stages of dementia (Scheltens, Fox, Barkhof, & De Carli, 2002). Voxel-based morphometry (VBM), a statistical method of assessing grey matter volume in MRI images, has identified reduced MTL volume in aMCI, with additional

volume loss in parietal and cingulate cortices in pAD (Karas, et al., 2004). Functional imaging techniques have provided other insights: positron emission tomography imaging using a glucose marker (FDG-PET) identified hypometabolism in posterior cingulate cortices, a junction between hippocampi and executive frontal regions involved in memory retrieval processes, in pAD and aMCI (Nestor, Fryer, Ikeda, & Hodges, 2003). Indeed, retrieval deficits in individuals with aMCI correlate with both hippocampal atrophy and posterior cingulate hypometabolism, whilst encoding difficulties correlate with hippocampal changes only (Chetelat, et al., 2003). Despite such useful insights into the pathological processes underlying MCI and AD, none of these markers have sufficient sensitivity and specificity in identifying those who will convert to pAD to be of real diagnostic benefit (Nestor, et al., 2004).

In contrast with structural and metabolic brain imaging, the two closely related non-invasive methods of electroencephalography (EEG) and magnetoencephalography (MEG) record electrical potentials and magnetic fields (respectively) that are a direct result of neuronal firing, which underpins the brain's computational and communicative functioning. The millisecond time resolution of these methods is far superior to other non-invasive functional imaging methods, enabling tracking in time of neural counterparts of rapid cognitive and sensory processes. Given that one feature of a system that is struggling (or compensating) in performing a cognitive task is likely to be a delayed neural response, this increased temporal resolution may offer greater sensitivity to more subtle changes in physiological function (before gross structural changes are apparent, for example in MRI). MEG is also unaffected by changes in the neurovascular coupling, that might occur with age and/or with dementia, but which would affect fMRI and PET measures.

The process of EEG/MEG recording is completely non-invasive, with no need for radioactive ligands or even the presence of a magnetic field (the latter being particularly important for patients with metal in their body, e.g, pacemakers or non-MRI-compatible stents, which become more common in old age). The minimal participant preparation and generally more comfortable setting involved in making an MEG recording in particular, make it especially amenable for use with patient populations. For example, a recent study successfully used MEG to identify potential biomarkers in patients with behavioural-variant fronto-temporal dementia (Hughes, Nestor, Hodges, & Rowe, 2011). Some EEG/MEG-based findings in Alzheimer's disease research are discussed later, after these methodologies are considered in more depth in the following section.

1.1.5 Section summary

Alzheimer's disease is a progressive neurodegenerative disorder, impacting upon multiple functional cognitive domains, that is hugely costly to both individuals and society. Mild cognitive impairment (MCI) describes a state of reduced cognitive function that may be an intermediate step in development of dementia, although many with this diagnosis will stabilise. MCI is defined primarily via clinical interview and poor performance on tests of cognitive ability, especially memory ability, in those at risk of AD. Neuropsychological testing, due to its behavioural nature, is vulnerable to confounds, such as strategy or anxiety. Neuroimaging techniques, as physiological tools, have offered insights into the disease process and may offer utility as more objective markers of disease. The temporal resolution of M/EEG is not available with any other non-invasive method, offering more direct insights into the neural activity underpinning mental processes. The following sections will describe this methodology in more detail, before discussing how it has been previously used in dementia research.

1.2 Magnetoencephalography (MEG)

The following section describes the neural origins and interpretation of neurophysiological signals detected by MEG and EEG.

1.2.1 Neuronal sources of MEG and EEG signals

Neurons typically consist primarily of a cell body (soma), multiple dendrites that convey incoming information to the soma and a single axon that carries outgoing action potentials. The basis of a neuron's ability to function as a computational unit is the perturbation, by inputs received from other neurons, of an electro-chemical gradient across the neuronal membrane and subsequent summation of these 'post-synaptic potentials' (PSPs), which may cause generation of an action potential. In short, MEG and EEG detect electrical currents and magnetic fields outside the head that result from this summation of PSPs when they are spatially aligned and temporally synchronised across many thousands of neurons.

More precisely, the neuronal membrane effectively divides the neuronal space into extra-cellular and intra-cellular compartments. In the resting state, the balance of ions, and therefore trans-membrane potential ('charge'), is maintained by highly energy-dependent ion pumps. When a neurotransmitter molecule binds to a receptor on the neuronal membrane, an ion channel opens and membrane permeability alters, in the case of excitatory receptors, allowing influx of positive ions and depolarising the membrane

potential. This is known as an excitatory post-synaptic potential (EPSP). These small depolarising currents both dissipate and summate over space and time, such that many simultaneously excited receptors or repeated excitation of the same population of receptors can result in a large depolarisation which is sustained over a timescale of tens of milliseconds. This is in contrast to action potentials that occur when depolarisation due to PSPs reaches sufficient magnitude (membrane potential of around +30mV) at the axon hillock, which are short-lived and of uniform amplitude.

In the case of cortical pyramidal neurons, whose elongated structure is such that their apical dendrites are quite distal to the soma and basal dendrites, EPSPs at the apical dendrites cause a potential difference to be set-up along the length of the neuron, resulting in dense intra-cellular (or 'primary') ionic current flow from the apical dendrites to the intra-cellularly more electro-negative soma and basal dendrites. Concurrently, positive ions flow through the extra-cellular space towards the apical dendrites, where the medium is more electro-negative, to close the current loop. This 'volume current' spreads out across the extra-cellular medium with the potential difference greatest along the shortest path from 'source' to 'sink', but dissipates with increasing path length, see *Figure 1.2*. A hyperpolarisation (inhibitory PSP) at the soma or basal dendrites would produce the same net direction of intra-cellular and volume current flow, although in these cases the current is driven by movement of negative ions. Thus M/EEG measurements do not differentiate between post-synaptic responses due to excitation versus inhibition (Hari, Parkkonen, & Nangini, 2010). MEG signals are mostly derived from the primary, intra-cellular currents, whilst EEG signals arise predominantly from volume currents; both reflect the same underlying process of neuronal activity.

PSPs produce current that is both unidirectional and of sufficient duration to overlap in time and thus summate across cells. Pyramidal cells, oriented perpendicular to the cortical surface, meet spatial requirements of proximity and parallel orientation to allow their individual currents to summate coherently. To produce electrical or magnetic fields outside the head of the magnitudes detected by M/EEG requires the summated contribution of tens of thousands of neurons from a patch of approximately at least $1cm^2$ of cortex (Hamalainen, Hari, Ilmoniemi, Knuutila, & Lounasmaa, 1993). This spatio-temporal super-position of activity in thousands of neurons produces a coherent macroscopic current flow. Meanwhile, action potentials are very brief and have leading and trailing edges oriented anti-parallel, cancelling one another (in all but the most rapidly conducting peripheral nerve fibres), so generate negligible electro-magnetic

signals distant from their source (Hari, et al., 2010; Williamson & Kaufman, 1990). To explain relationships between currents generated in neural tissue and the M/EEG signals recorded external to the head, it is convenient to use the simple approximation of representing the average current source in a small area of active cortex as an 'equivalent current dipole' (ECD). The ECD is a vector, having orientation and position and is often represented by an arrow pointing in the direction of the current, with current inflow at the tail and outflow at the head of the vector. The dipole moment, 'Q', is the product of the current amplitude (I) and the length and direction in which it travels ($\vec{L}$): $Q = I\vec{L}$ (Lu & Kaufman, 2003; Williamson & Kaufman, 1990). As the ECD is a composite of many neural currents in proximity, some flowing in opposite directions, the exact strength and extent of neuronal activation cannot be easily derived from the dipole moment (Hari, et al., 2010).

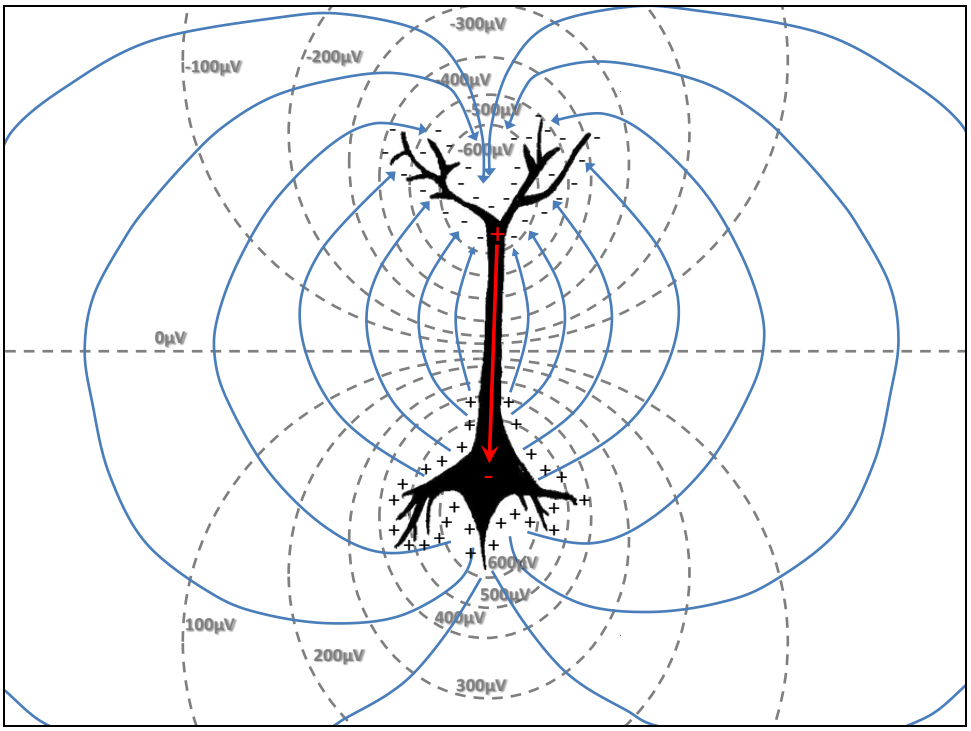


Figure 1.2: Neuronal intra-cellular and volume currents

A depolarising current is set up at distal dendrites in a cortical pyramidal neuron, a dense intra-cellular ionic current flows from positive to negative (red arrow), whilst an extra-cellular ionic 'volume' current flows from positive to negative dispersed throughout the surrounding medium (blue arrows).The dashed grey contour lines represent electrical potential which varies according to distance and orientation from the current source (neuron). The magnetic field (not shown) emerges from the right side of the page and enters at the left side, but is not detectable in the plane that is perpendicular to the direction of the source.

1.2.2 Characteristics of magnetic and electrical fields

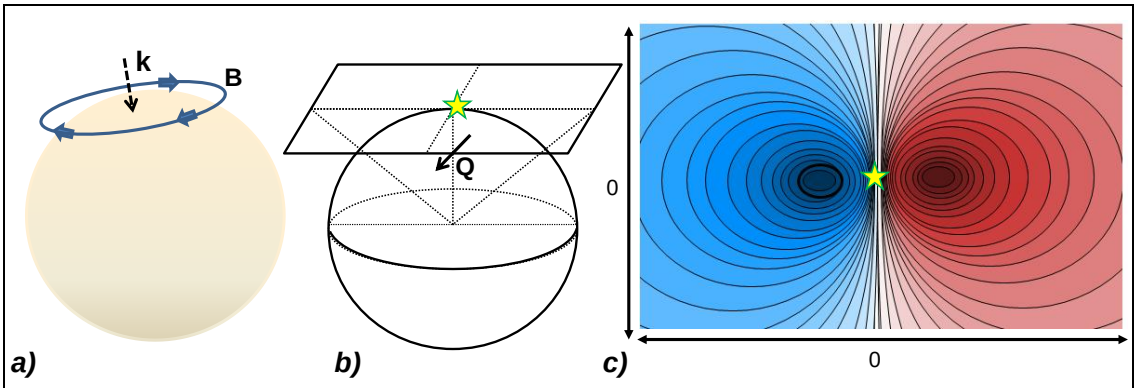
The magnetic field produced by a current dipole lies in a plane perpendicular to the current orientation and the direction of this field follows a clockwise course where the dipole is orientated away from the observer[1] (see *Figure 1.3* for examples), thus measured from the surface of a sphere the magnetic field has both outward and inward maxima. The magnetic field is strongest at a 90° angle from the direction of current and diminishes to zero in the direction of current flow. The magnetic flux density, 'B', or field strength, is proportional to the dipole moment (strength) Q and decreases (non-linearly) as the square of the distance from the dipole. This means that sensitivity of MEG decreases rapidly with distance from a current source and it is not effectively able to detect activity arising from sub-cortical structures or from cortical surfaces when they are not sufficiently close to the sensor array.

The component of the magnetic field that is tangential to MEG sensors cannot be measured. Therefore a source at the centre of a sphere, the surface of which is surrounded by sensors aligned tangential to that surface, cannot be detected. Likewise, the radial component of a current dipole at any other position within the sphere cannot be measured. While the head is not a perfect sphere, this effect is evident when using realistic head models; there are dramatic differences in MEG sensitivity at different locations, dependent upon the source orientation (Ahlfors, Han, Belliveau, & Hamalainen, 2010). As only the tangential component of current sources are visible to MEG, these are detected primarily from sulcal and fissural walls (Molins, Stufflebeam, Brown, & Hamalainen, 2008). As the field occurs in a circular plane perpendicular to the current source, when sampled along the surface of a sphere the radial magnetic field demonstrates outward and inward maxima distal to the ECD source (*Figure 1.3b*). The point intermediate to these maxima, which is where radial field power changes most rapidly across the tangential plane (see proximity of isofield contour lines in *Figure 1.3c*), is situated directly above the dipolar source (*Figure 1.3b*).

This insensitivity of MEG to tangential fields can be viewed as an advantage, in helping to reduce the sensitivity of MEG to volume (extra-cellular) currents; the magnetic field detected distant from a source is comprised mainly of contributions from the primary (intra-cellular) current. One reason is that, despite the volume currents being

[1] Magnetic field direction can be predicted by the *'right-hand rule'*, that is, if the thumb of the right hand points in the direction of current flow, the direction of the field follows the curved fingers.

substantial, they are far less dense than the intracellular current, and also display radial symmetry, therefore producing no net magnetic field as the symmetrical contributions cancel each other (Williamson & Kaufman, 1990). Another reason relates to the interactions of the volume currents with the boundary of the inner skull surface (when a boundary is encountered, current density is increased along the high- relative to low-conductivity side of the boundary in order to maintain the electrical potential along the boundary, which results in generation of a secondary current): as the associated magnetic field is largely tangential to the sensors outside the boundary (*Figure 1.3a*), these secondary effects are largely unseen by MEG, unlike EEG. Furthermore, magnetic fields, unlike electric fields, pass through the tissues of skull and scalp unimpeded, therefore virtually undistorted, prior to their detection external to the head. These are some of the reasons why the sources of MEG signals are easier to localise than those of EEG signals (though such localisation is still not trivial).



Adapted from Williamson & Kaufman (1990); Lu & Kaufman (2003)

Figure 1.3: Neuromagnetic fields beyond the scalp

a) *Secondary current sources (k) arising from interaction of volume currents with the scalp boundary produce a tangential magnetic field (B); b) Single tangentially-oriented dipolar intra-cerebral source (Q), star marks point on scalp immediately above source; c) Topographical map depicting magnetic field pattern produced by dipolar source Q, red = field directed out of the head, blue = inwards directed field, darker colours = greater field power.*

The volume currents that largely comprise the EEG signal flow in the opposite direction to their source dipole, in order to close the current loop (*Figure 1.2*). Electrical potentials measured at the scalp comprise both tangential and radial components, although EEG tends to record the strongest signals from gyral crests. This is because, firstly, tangentially-oriented dipoles on sulcal walls subtend a more acute solid angle when 'viewed' from an electrode positioned on the scalp surface than radially-oriented dipoles in gyral crests, and, secondly, volume currents arising from dipoles on opposite

sulcal walls act to cancel one another (Gloor, 1985). Hence MEG and EEG detect largely complementary information, and optimal ability to localise sources of activity is achieved when these methods are combined (Molins, et al., 2008). Scalp topographies can be complex even for a single ECD and the relation of EEG signals to their dipolar sources is further complicated by the varying impedances of the cerebral matter, tissues of skull, scalp and cerebro-spinal fluid that form a unique combination in any given individual. As the conductivity of the skull is around 80 times lower than that of the brain, this causes the current flow and subsequently electrical potential measured at the scalp to be attenuated and 'smeared' to variable extent dependent upon the relative orientation of the dipole (Gloor, 1985). This makes construction of an accurate 'lead field', the activation pattern detected at the sensors for activity of a dipolar source for each location and orientation, challenging for EEG and impossible without a boundary element head model that accurately incorporates brain, inner skull and scalp boundaries. An MEG forward model for the lead field on the other hand, is far more robust to deviations from the spherical head model and can be computed using spherical head models at a much lower computational load (Hamalainen, et al., 1993; Molins, et al., 2008). As a result, when a single modality is recorded, for superficial sources at least, MEG gives far higher spatial resolution and reduced error in identifying likely sources of activity (Molins, et al., 2008). The proper way to estimate such sources involves solving the 'inverse problem', though this has no unique solution, and requires making a number of assumptions and numerical approximations that are beyond the remit of this thesis.

1.2.3 Sensor types and sensitivities

Signal amplifiers, digital-to-analogue conversion and computers are now essential components of both EEG and MEG systems. The following section describes sensors that are used to detect the signals and constraints imposed on their interpretation.

1.2.3.1 EEG electrodes

EEG electrodes attached to the scalp take time to apply, as it is often necessary to exfoliate the scalp to establish good contact. Unlike MEG, EEG is irrevocably reference-dependent as measurements must be made relative to a reference electrode, which may be at a single location (e.g. nose or vertex) or an arithmetic mean of multiple electrodes (e.g. bilateral mastoids or whole-head). This reference may be selected to optimise sensitivity to a particular EEG component.

1.2.3.2 Superconducting quantum interference devices (SQUIDs)

MEG has the advantage of being 'reference-free' and does not involve time-consuming scalp preparation. However, the tiny neuromagnetic fields are around 1 billionth of the strength of the Earth's magnetic field and far smaller than environmental sources of electromagnetic 'noise', thus requiring extremely sensitive sensors. These sensors, SQUIDs (Superconducting QUantum Interference Devices), are made of superconducting materials that when cooled to 4.2˚K (via the use of liquid helium)provide zero resistance to current flow. Once the sensors, located inside a cryogenic dewer, are cooled to the superconducting state, a change in current flow in the detection coil(s) is produced by even the tiniest perturbation in the ambient magnetic field. This current flow is transferred via a detector ("pick-up") coil to the SQUID, which converts the current to a voltage output that is subsequently amplified and digitised to produce the MEG signal (ElektaNeuromag, 2005; Lu & Kaufman, 2003). Spatial sensitivities of SQUID sensors vary according to the configuration of detection coils, as outlined below.

1.2.3.2.1 Magnetometers and axial gradiometers

A magnetometer is comprised of a single detection coil, making it sensitive to any external magnetic fields perpendicular to its surface (see *Figure 1.4a*). This ability to respond to fields of uniform gradient confers sensitivity to more distal magnetic sources that may arise from deeper (potentially even sub-cortical) brain structures; however it is also therefore more susceptible to effects of ambient noise and less able to spatially localise magnetic sources.

The simplest type of axial gradiometer, a first order axial gradiometer, consists of two coils wound in series such that current flow is anti-parallel between the two coils. Thus flow in the second coil is effectively subtracted from that in the first, cancelling out distal magnetic sources and improving ability to pinpoint the source of a nearby signal. In effect, the axial gradiometer measures the spatial derivative of the field in the radial direction. As noted above, absolute field strength is maximal at locations displaced from its source dipole; therefore no simple inferences can be made on the basis of magnetometer or axial gradiometer field patterns as to source origins and computational solutions are required.

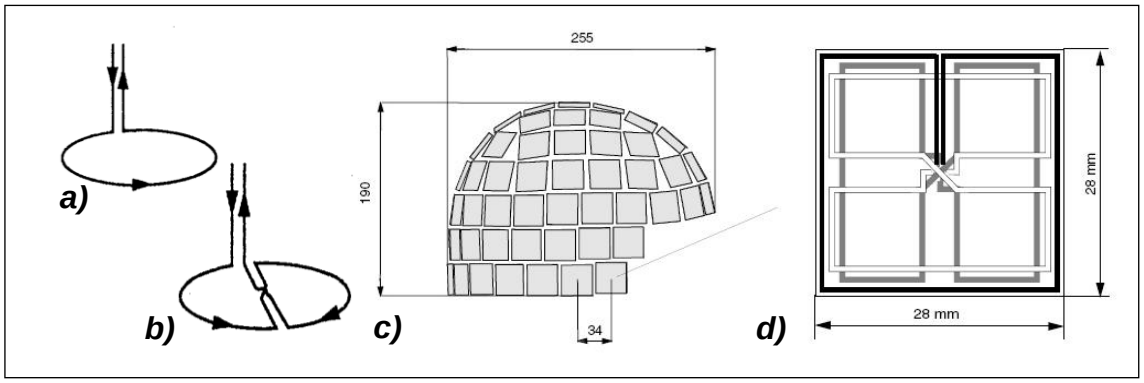


Figure 1.4: Types of SQUID detection coil
a) Magnetometer; b) Planar gradiometer; c) Helmet-shaped array of 102 sensor locations in Elekta Neuromag VectorView MEG system; d) Triple sensor detector unit, comprised of a pair of planar gradiometers (grey and white) with sensitivity to orthogonal spatial derivatives of the magnetic field, and one magnetometer (black) with sensitivity to deeper sources, as implemented in the Elekta Neuromag VectorView System (c.f. ElektaNeuromag, 2005).

1.2.3.2.2 Planar gradiometers

A planar gradiometer is comprised of 2 coils wound in opposite directions in a single plane (see *Figure 1.4b*), enabling it to measure the spatial derivative of the field in a tangential direction, that is changes in the magnetic field across the surface of the scalp. A second planar gradiometer placed orthogonally in the same location allows the 2 independent gradient components to be combined to provide a measure of both local field magnitude and orientation (Lounasmaa & Hari, 2003). The Elekta Neuromag MEG system used in the current study comprised a combination of 2 orthogonally positioned planar gradiometers (*Figure 1.4d*), for optimum localizability of sources, and a single magnetometer (for sensitivity to deeper sources), at 102 locations covering head surface using a helmet-shaped array (*Figure 1.4c*), resulting in a 306-channel system with complimentary sensor types. Importantly, planar gradiometers detect maximal magnitude where field power changes most rapidly, immediately above a magnetic source (Hamalainen, et al., 1993), providing meaningful and easily interpretable topographical information, even without application of complex computational methods.

One way to represent this topographical information is to calculate a scalar measure of total gradient magnitude at each sensor location, such as root mean squared (RMS) magnitude of the two orthogonal gradiometers ($RMS = \sqrt{\frac{{g_1}^2+{g_2}^2}{2}}$ where g_1 and g_2 are signal magnitudes of planar gradiometers at the same location with sensitivity to orthogonal directions of the field's spatial derivative). The signal orientation information is lost but this method ensures that signal magnitudes of all orientations are treated

equally. As the RMS rectification procedure makes all values positive, any zero-mean noise in the original gradiometer data is no longer reduced (cancelled) when averaging across trials. Therefore, in the present analyses, the gradiometer data for each trial (epoch) were averaged across trials first, before taking the RMS, and then subsequently re-baseline-corrected. Conditions containing more trials will also tend to have a smaller RMS, given greater cancellation of noise during the prior averaging, and therefore contrasts across RMS-rectified conditions are valid only when there are approximately equal numbers of trials for each condition. For this reason, in the passive paradigm described in chapters 6-9, when computing the difference between 'frequent' and 'infrequent' conditions, we equalised trial numbers by pseudo-randomly selecting a subset of frequent trials. We used this 'difference-in-RMS' approach to construct sensor-level statistical parametric maps (SPMs) to characterise within-group MEG effects for our primary contrasts in young and older control groups. However, the approach is invalid if there is greater noise across trials (and/or time points) for one group than another (for example, patients versus controls). The alternative approach, which we used for subsequent single-sensor-level contrasts, is to calculate the contrast of conditions before taking the RMS of the result ('RMS of difference'); this allows the noise components of signals in both conditions to cancel one another before rectification transforms them to positive, although this loses information regarding the direction of the magnitude difference between conditions.

1.2.4 Summary of M/EEG basics

The fields/potentials detected by M/EEG sensors result from summation of synchronous post-synaptic membrane depolarisations and repolarisations across many thousands of individual neurons. The chief sources of MEG signals are intra-cellular currents that flow when a potential difference is set-up across an individual neuron as a result of post-synaptic depolarisation, whilst EEG signals are mainly derived from the corollary 'volume currents' that arise in the extra-cellular space. The elongated structure of cortical pyramidal cells means they are most able to exhibit these potential differences and thus are the primary source of M/EEG signals.

Super-imposed currents from thousands of neurons create a coherent current flow; for simplicity this can be thought of as an equivalent current dipole, with attributes of strength and direction. The magnetic field produced by such a dipole lies in a plane perpendicular to the direction of current and decreases rapidly with distance from the

current source. The magnetic fields produced by volume current sources, which display radial symmetry, cancel one another entirely; likewise, fields produced by interaction of volume currents with the inner skull surface are tangentially-oriented, meaning that, unlike EEG, only intra-cellular primary current sources that are oriented parallel to the inner skull are visible with MEG. EEG is most sensitive to sources in gyral crests, whereas sources of MEG are located primarily in sulcal walls; the two methods are therefore largely complimentary. Whilst sensitivity to MEG signals declines more with distance than that of EEG signals (given the increasing radial component of dipoles located closer to centre of a sphere), absence of interactions with skull and scalp boundaries makes resolution of contributing sources much simpler. The next sections describe some studies that have employed these methods and how they may be applicable to diagnosis of dementia.

1.3 M/EEG studies of semantic and episodic memory in pAD and MCI

The following section outlines the effects of repetition and semantic context on two ERP components, the so-called 'N400' and 'P600', which are believed to be reflective of memory processes and have demonstrated sensitivity to pAD. These potential biomarkers form the basis of the active memory paradigm employed in this thesis (chapters 2-5). We further review what is known about their modulation with 1) age and 2) MCI/AD.

1.3.1 The N400(m) response: Contextual integration

The N400 is a scalp-negative EEG component that peaks at around 400ms after the occurrence of potentially semantically meaningful stimuli (such as words or pictures) and is of greatest magnitude when the stimulus is unexpected. N400 response magnitude to a word is enhanced with lower expectedness (or 'cloze probability') given a preceding sentence context, with largest responses to nonsense words, followed by unexpected words, then expected words and smallest responses to the most probable sentence ending word (Federmeier & Kutas, 1999), see *Figure 1.5*. Likewise in MEG, magnitude of the N400 magnetic counterpart (N400m) was shown to increase for semantically incongruent relative to congruent words (Halgren, et al., 2002). The N400(m) is thought to index a general semantic or 'contextual' integration process, with magnitude modulated by the relative ease or difficulty of integration with existing representations of meaning (Hagoort, 2008; Kutas & Federmeier, 2000). It is not an effortful conscious process, as the effect remains even when the preceding 'context' is a masked word that is not

consciously perceived (Kiefer, 2002). The reduction of the N400(m) by preceding semantically related context can also therefore be seen as a neurophysiological correlate of semantic priming[2].

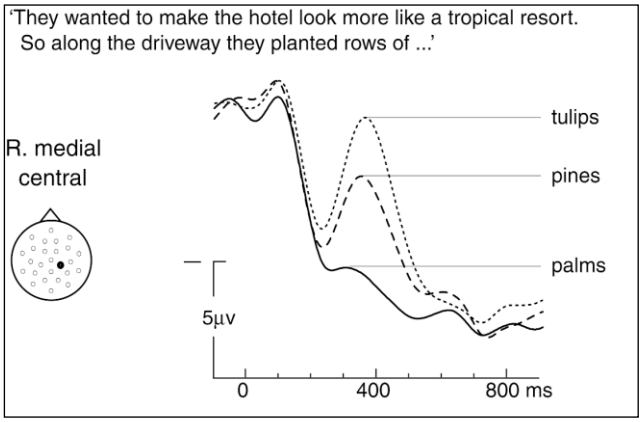


Figure 1.5: Modulation of N400 amplitude by cloze probability
Cited from Federmeier & Kutas,(1999)

1.3.1.1 N400(m) semantic congruency effect

The subtraction of responses to congruent from those to incongruent category exemplars yields such an N400(m) congruency effect (Kutas & Hillyard, 1982). Studies in brain-injured and epileptic patients have shown that a functionally intact left (but not right) temporal lobe is necessary for the effect (Friederici, Hahne, & von Cramon, 1998; Olichney, Riggins, et al., 2002), although the scalp EEG distribution has a right hemispheric emphasis (Kutas & Hillyard, 1982), which stresses the inherent difficulty in interpreting topographical EEG data in terms of underlying neural generators. In MEG, the effect has been localised to widespread, predominantly left hemispheric, sources incorporating fronto-temporal, orbito-frontal, perisylvian and dorso-lateral pre-frontal cortices (Halgren, et al., 2002), convergent with intra-cranial recordings (Halgren, et al., 1994b; McCarthy, Nobre, Bentin, & Spencer, 1995) .

In normal ageing, the magnitude of the N400 congruency effect decreases and its peak latency increases, with both measures becoming more variable, perhaps attributable to cortical thinning and/or associated reduced processing efficiency (Head, Rodrigue,

[2] Behaviourally, priming reflects the facilitation of reproduction of a stimulus, or a reduction in errors/response times in responding to a stimulus, after prior exposure to either the same, or a related (semantic/associative priming), 'prime' stimulus, even in the absence of conscious recollection of prior exposure (Henson, 2003).

Kennedy, & Raz, 2008). Topographical distribution does not differ according to age, suggesting that processes underlying the congruency effect are qualitatively similar across the lifespan (Kutas & Iragui, 1998).

The congruency effect in patients with pAD has tended to be reduced in magnitude and delayed to an extent beyond that seen in healthy ageing (Castaneda, Ostrosky-Solis, Perez, Bobes, & Rangel, 1997; Taylor & Olichney, 2007) as might be expected given a degradation of semantic memory. The overall pattern of N400 response modulation remains intact, that is, response magnitude to sentence-ending words is still modulated by cloze probability (Hamberger, Friedman, Ritter, & Rosen, 1995), implying that despite overall degradation of N400 responses, semantic organisation remains relatively preserved. The finding that the N400 congruity effect was present (although reduced) in some pAD patients when words were preceded by pictures, regardless of whether or not the individual had been able to name the pictured object (Ford, et al., 2001) suggested that semantic knowledge was sufficiently intact to facilitate contextual integration processes even when the name could not be explicitly retrieved. Overall, these point to a combination of both retrieval deficits and degraded semantic representations as the bases of semantic deficits in pAD.

1.3.1.2 N400(m) repetition effect

The N400 is also reduced when an item is repeated (Rugg, 1985); this repetition effect is sensitive to lag, becoming smaller with increasing delay between presentations (Van Petten, Kutas, Kluender, Mitchiner, & McIsaac, 1991). The effect was shown to be maximal when words were repeated within the same (incongruent) context (following an intervening cued recall task), indicating some effect of semantic context (Besson & Kutas, 1993). That this effect remains intact in amnesiacs with damage to medial temporal lobe regions who have no conscious recollection of having seen the word previously (Olichney, et al., 2000) adds support to the view that this is primarily an ‘implicit’ semantic priming effect (rather than an episodic memory effect; see below), temporarily facilitating availability of word meaning and therefore contextual integration (Kutas & Federmeier, 2000). This may be conceived of in a somewhat similar vein to N400 word frequency effects, whereby (sentence intermediate) words with higher lexical frequency evoke smaller N400 magnitude, presumably due to greater ease in accessing word meaning (Kutas & Federmeier, 2000).

In contrast to findings in MTL amnesiacs, the N400 repetition effect is reduced in pAD (Olichney, et al., 2006), with N400 amplitude less reduced by repetition than in healthy aged-matched controls. When this effect was studied in patients with MCI, it was found not to significantly differ from controls (Olichney, Morris, et al., 2002), however, follow-up analysis comparing converters and non-converters found the repetition effect to be absent in converters only (Olichney, Taylor, Gatherwright, et al., 2008), suggesting potential as a biomarker of subsequent conversion to pAD.

1.3.2 The P600(m) response: Episodic memory

Another ERP component that is sensitive to repetition of items, but in this case is also associated with conscious recollection, is the late positive component (LPC) otherwise known as P600, given its peak latency of around 600ms and scalp positive polarity. This component is not to be confused with the P600 known in neurolinguistic research as syntactic positive shift (SPS), which is sensitive to syntactic/grammatical violations and ambiguities in sentences (Hagoort, Brown, & Groothusen, 1993). When using lists of single words in an explicit test of recognition memory, the LPC P600 tends to be greater for repeated relative to initial presentation of words, particularly for those words clearly recollected (Nagy & Rugg, 1989; Rugg, 1985; Woollams, Taylor, Karayanidis, & Henson, 2008). Furthermore, during the initial study of words in such recognition memory paradigms, the P600 component is also greater for words that are subsequently recognised in the test phase than for those that are subsequently forgotten, particularly when encoded semantically (Fernandez, et al., 1998; Paller & Kutas, 1992; Paller, Kutas, & Mayes, 1987); see *Figure 1.6a*.

However, when an item is repeatedly presented within a congruent semantic context, the P600 is actually reduced in magnitude (Besson, Kutas, & Van Petten, 1992; Olichney, et al., 2000); see *Figure 1.6b*. This reduction is referred to henceforth as the P600 congruent repetition effect. The P600 component is believed to reflect the process of retrieving the contents of long-term memory into working memory (Burkhardt, 2007; Van Petten, et al., 1991). This can explain the P600 increase when a single word is recollected from a previous study phase, but its decrease when a word is already active in working memory owing to repetition of a predictive (congruent) sentence context. The P600 also appears sensitive to repetition lag, decreasing in magnitude (Henson, Rylands, Ross, Vuilleumeir, & Rugg, 2004), or peaking later (Karayanidis, Andrews, Ward, & McConaghy, 1991) with increasing lag in item-lists, though others found no significant

effects of lag in either item-lists, ranging from 0 to 19 items (Nagy & Rugg, 1989), or semantic contexts, ranging from 10-40s (Olichney, et al., 2000).

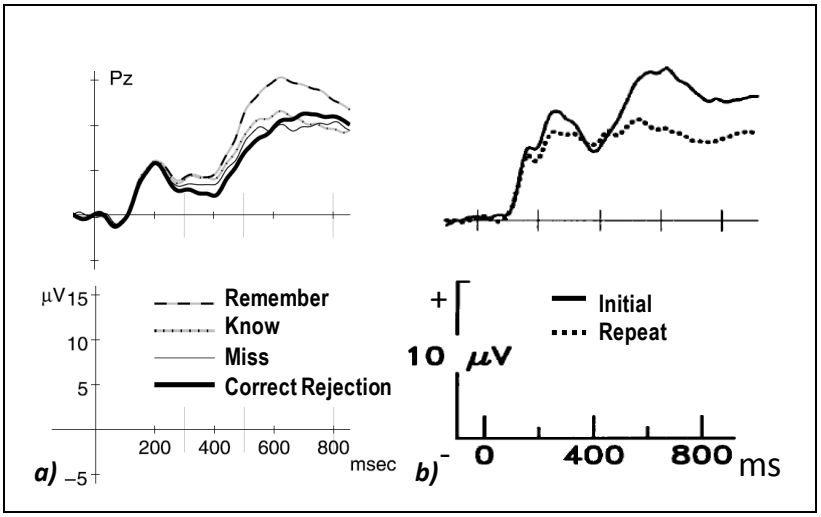


Figure 1.6: The P600 and repetition

a*) During a test of recognition memory for single words, the P600 component was larger for items that were remembered, compared to those that were not recognised, or just seemed familiar (c.f. Woollams, et al., 2008). Shown at midline parietal electrode Pz. b) During a congruency judgement task, on the other hand, the P600 was reduced upon repetition of congruent items (c.f. Olichney, et al., 2000). Shown at a left temporo-parietal electrode Wl.*

The P600 and N400 repetition effects appear to have different underlying generators, as evidenced by their differential decrement in MTL amnesia (e.g, Olichney, et al. 2000 found only the P600 repetition effect to be absent in amnesiacs) and by depth electrode recordings (where P600 sources included the hippocampus, and entorhinal, cingulate, anterior temporal and orbito-frontal cortices, which were largely distinct from, although with some overlap with, those of the N400; (Halgren, Baudena, Heit, Clarke, & Marinkovic, 1994a). Nonetheless, at the level of scalp EEG recordings, the P600 congruent repetition effect overlaps both temporally and spatially with the N400 repetition effect. This problem is elegantly circumvented by a paradigm adapted by Olichney and colleagues (2000, 2002, 2006, 2008), which crosses factors of congruity and repetition. A single trial consists of a category phrase, presented auditorily, followed by a visual word that is either congruent or incongruent with the category, and these trials are then repeated at variable intervals. As the N400 component is virtually eliminated in the initial congruent trial, the contrast of initial versus subsequent repetition of congruent trials enables the P600 repetition effect to be isolated from the N400 repetition effect. Using this paradigm, the P600 congruent repetition effect has been shown to correlate positively with behavioural measures of episodic memory, such as neuropsychological memory scores and recall of items within the paradigm (Besson, et al., 1992; Olichney, et

al., 2006; Olichney, Morris, et al., 2002; Olichney, et al., 2000).

Although declarative memory declines in many older individuals *(Wilson, et al., 2002),* differences in P600 magnitude or latency between young and elderly subjects have not been previously examined. Using the above congruity-repetition paradigm in fMRI however, it was found that older individuals who performed above median on a subsequent recall task had markedly greater extent and magnitude of left medial temporal lobe and fusiform gyrus activation for the contrast of new congruent words minus repeated congruent words (Olichney, Taylor, Hillert, et al., 2008). Thus, although there are no overall age-related differences in P600 congruent repetition effect, it appears that older adults with better declarative memory performance recruit its putative underlying generators to a greater extent than those who perform poorly.

In mild pAD cases, the P600 congruent repetition effect was shown to be absent (Olichney, et al., 2006), as was its fMRI counterpart (Olichney, et al., 2010), and in both cases the magnitude of the effect correlated with memory performance. In those diagnosed with MCI, the P600 word repetition effect was reduced, with its presence accounted for almost entirely by those who did not subsequently convert to dementia (Olichney, Morris, et al., 2002). The presence of reduced P600 congruent repetition effect and/or N400 incongruent repetition effect was a highly accurate predictor of conversion to pAD within 3 years, with 87% positive predictive value (i.e. 87% of those who met this criterion developed dementia) and 88% negative predictive value - that is, 12% of those who did *not* meet this criterion developed dementia (Olichney, Taylor, Gatherwright, et al., 2008).

1.3.3 Summary – ERP measures of semantic and episodic memory

N400 semantic congruity and N400 and P600 repetition effects are well established markers of semantic memory, semantic priming and episodic memory, respectively. All have shown alterations in individuals with dementia, distinct from those associated with normal ageing. N400/P600 repetition effects and their combination in particular show promise as sensitive markers of incipient dementia, as investigated in chapters 2-5.

1.4 The mismatch negativity to spoken words and auditory P50(m)

The following section describes background literature pertinent to the phenomenon of sensory gating, reflected in habituation of the P50(m) 'obligatory' acoustic response, and to the linguistic mismatch negativity (MMN(m)), the bases for the passive paradigm

employed in this thesis (chapters 6-9). Their modulation according to 1) age and 2) MCI/AD is also reviewed.

1.4.1 Spoken word mismatch negativity (MMN(m))

The mismatch negativity (MMN) and its magnetic counterpart (MMNm) are passively-evoked automatic brain responses to the occurrence of an infrequent (so-called 'deviant') stimulus within the context of frequent ('standard') stimuli. The MMN, calculated as a deviant minus standard difference wave, was suggested to index automatic *discrimination* of acoustic stimulus features, as opposed to purely acoustic characteristics, even in the absence of attention (Naatanen, 2001; Naatanen, Kujala, & Winkler, 2011). The MMN(m) cannot be elicited before regular characteristics of the 'standard' stimulus have been established in working memory, which requires multiple standard repetitions (Bendixen, Prinz, Horvath, Trujillo-Barreto, & Schroger, 2008). It has been proposed to reflect neuronal adaptation, whereby auditory cortex neurons become adapted to a repetitive stimulus until a deviant occurs (Jaaskelainen, et al., 2004), as well as release from tonic inhibition (Naatanen, 1990), which both could be a basis for a neural automatic change detection mechanism linked to short-term synaptic plasticity (Sussman & Winkler, 2001; Winkler, Karmos, & Naatanen, 1996). In addition to automatic auditory discrimination and change detection, MMN(m) has been linked to more complex, cognitive processes triggered in the cortex by information present in infrequent deviant sounds. That an MMN(m) occurs in response to violation of abstract rules in complex sequences, even when individual acoustic stimuli are equally probable, has been interpreted as a reflection of a 'primitive intelligence' in the auditory system (Paavilainen, Arajarvi, & Takegata, 2007). Furthermore, a larger MMNm is elicited by the same phoneme, when it is part of subject's native phonological system that when it is not (Naatanen, et al., 1997) and likewise a larger MMN(m) is exhibited for the same syllable completing a meaningful word compared to a meaningless pseudoword, an effect not found in non-native speakers (Pulvermuller, et al., 2001). Such studies argued against the MMN(m) being due solely to neuronal adaptation. Indeed, enhanced magnitude of MMN(m) responses for words relative to pseudowords (see *Figure 1.*7 for an example) have been argued to rely crucially on activation of long-term memory traces for the words (Naatanen, 2001; Pulvermuller & Shtyrov, 2006; Shtyrov, Pihko, & Pulvermuller, 2005; Shtyrov & Pulvermuller, 2002), this has gained support from neural network computer simulations (Garagnani & Pulvermuller, 2011). Spoken word MMN(m) studies have

additionally probed these linguistic memory traces to show pre-attentive sensitivity to violations of syntactic properties (Pulvermuller & Shtyrov, 2003; Shtyrov, Pulvermuller, Naatanen, & Ilmoniemi, 2003) and even to incongruent semantic context (Shtyrov & Pulvermuller, 2007).

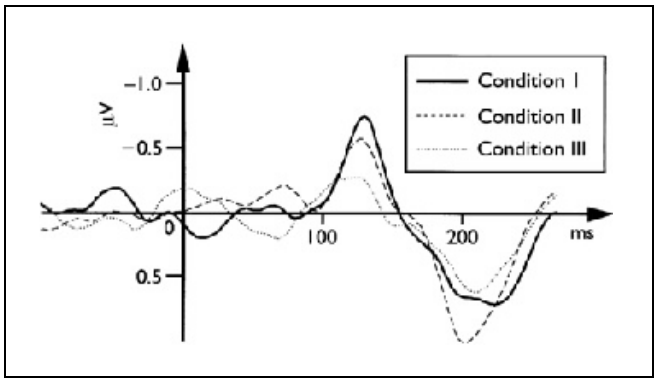


Figure 1.7: MMN to words versus pseudoword
Significantly larger MMNs (128-148ms) occurred for word deviants (conditions I and II) relative to a pseudoword deviant (condition III) at midline fronto-central electrode FCz (c.f. Shtyrov & Pulvermuller, 2002).

The MMN(m) is particularly suitable for examining responses depending upon these long-term memory traces and especially within patient groups for reasons detailed below:

1. The MMN(m) is early, typically occurring in the range of 100-200ms post-stimulus, which is within the time range suggested by behavioural work that linguistic processing begins (Marslen-Wilson & Tyler, 1975; Sereno & Rayner, 2003; Zwitserlood, 1989). Early obligatory auditory responses (P50(m), N1(m)) have not been previously linked to abstract stimulus features such as lexical status, or sequence position. Other neurophysiological components related to lexical/semantic processing, such as the N400 discussed earlier, occur much later, and are therefore likely to reflect consequences of comprehension processes rather than initial lexical/semantic processes themselves. It may be that such earlier neurophysiological indices are more sensitive to mechanisms underlying subtle language or memory impairment in conditions such as mild Alzheimer's disease and MCI and less influenced by compensatory mechanisms.

2. The MMN(m) is automatic, occurring in the absence of stimulus-directed attention. This confers advantages of freedom from strategic and attentional confounds, which are particularly relevant in the context of studies involving cognitively-impaired patients, where task-comprehension and focus may comprise some difficulties. Indeed, the MMN paradigm has been used in a variety of clinical contexts, for example in studies of

schizophrenia (Baldeweg, Klugman, Gruzelier, & Hirsch, 2004) and even with comatose patients, whence it has proven a useful predictor for recovery of consciousness (Fischer, Luaute, Adeleine, & Morlet, 2004; Wijnen, van Boxtel, Eilander, & de Gelder, 2007).

3. Effect of physical stimulus features can be controlled, at least partially, by using the subtraction paradigm. Using an identical stimulus as a deviant across different contexts (e.g. */t/* deviant added to standard stem *'play'* produces either a meaningful word *'plate'* or a meaningless pseudoword *'kwate'* if added after *'kway'*), means that acoustic properties of the standard-deviant contrasts can be exactly matched across conditions. When the neurophysiological response to the standard stimulus is subtracted from that to the deviant, any remaining difference across the conditions can be attributed to the diverging contexts and not to acoustic properties as such.

4. Minimal stimulus variance and subsequent improved signal to noise ratio is obtained by focusing on responses to individual stimuli. This is because differences in physical features of stimuli, and psycholinguistic properties in the case of linguistic stimuli, as might be the case for multiple items in a large stimulus group, can lead to differential activation and smearing of effects across time, masking early linguistic effects.

MMN(m) responses to non-linguistic stimuli were found to reduce in magnitude with increasing age, and this cannot be explained by underlying differences in the N1(m) auditory response (Czigler, Csibra, & Csontos, 1992; Gaeta, Friedman, Ritter, & Cheng, 1998; Kiang, Braff, Sprock, & Light, 2009; Schiff, et al., 2008). Elderly participants in behavioural tasks were able to detect occurrence of small frequency deviants (Gaeta, et al., 1998) and gap duration deviants (Bertoli, Smurzynski, & Probst, 2002), despite elderly groups producing no MMN to the same deviants. This MMN(m) reduction therefore seems to reflect poorer sensory memory representations in older than young individuals, as opposed to an inability to detect the change. Some authors have found greater MMN reduction with longer ISI, suggesting more rapid degradation of sensory memory traces in elderly relative to young participants (Pekkonen, 2000; Pekkonen, Jousmaki, Partanen, & Karhu, 1993).

Although an MMN magnitude decrement in pAD patients relative to age-matched controls has not been reliably detected at ISIs of one second or less (Bronnick, Nordby, Larsen, & Aarsland, 2008; Gaeta, Friedman, Ritter, & Cheng, 1999; Kazmerski, Friedman, & Ritter, 1997), it does emerge at longer ISIs. This suggests an exacerbation of the faster rate of sensory memory decay found in healthy elderly participants, rather than a deficit in acoustic change detection (Pekkonen, 2000; Pekkonen, Jousmaki, Kononen,

Reinikainen, & Partanen, 1994; Yokoyama, Nakashima, Shimoyama, Urakami, & Takahashi, 1995). As central cholinergic antagonists reduce MMN magnitude, depleted cortical cholinergic transmission in AD may be a cause of more rapid sensory memory decay (Pekkonen, Hirvonen, Jaaskelainen, Kaakkola, & Huttunen, 2001). The linguistic version of the MMN(m) has not previously been examined in pAD patients; it is likely that the ability of such a paradigm to 'tap into' long-term memory traces for psycholinguistic properties would provide sensitive markers of memory and language processing impairments. This and its task-free, automatic nature make the linguistic MMNm paradigm a particularly suitable potential candidate for use in identifying biomarkers of dementia.

1.4.2 P50(m) 'obligatory' auditory response and sensory gating

The P50(m) is an obligatory acoustic response generated in posterior superior temporal sulci (Knott, Millar, & Fisher, 2009; Korzyukov, et al., 2007) in response to any auditory stimulus, in the presence or absence of attention. The scalp EEG P50 contains additional contributions from deeper sources (Huotilainen, et al., 1998). When auditory stimuli are presented in succession, at a rate of more than approximately one per 8 seconds (Boutros, et al., 1995; Ermutlu, Demiralp, & Karamursel, 2007; Zouridakis & Boutros, 1992), habituation occurs and the second and subsequent stimuli are reduced in magnitude. This P50(m) suppression is believed to reflect 'sensory gating', pre-attentive modulation of the brain's sensitivity to incoming stimuli, in this case 'gating out' and reducing salience of less relevant sensory information (Boutros & Belger, 1999; Braff & Geyer, 1990). This effect has been widely studied in schizophrenic individuals and found to be reduced (i.e. magnitude of the second stimulus is reduced less, so relatively larger) in comparison with control participants, possibly relating to the sensation of 'sensory overload' that can be a feature of this disorder (Patterson, et al., 2008). Similarly, 'gating in' refers to the enhancement of the P50(m) response that occurs to more salient stimuli. For example, in oddball paradigms, P50 responses to infrequent stimuli were enhanced relative to those to frequent 'standard' stimuli (Boutros & Belger, 1999; Boutros, et al., 1995; Rosburg, et al., 2004), see *Figure 1.8*. However, interactions of long-term memory traces with sensory gating, such as comparing known words with unfamiliar pseudowords, have not been examined before.

The magnitude of basic P50(m) responses increases in older age (Golob, Irimajiri, & Starr, 2007; Pekkonen, et al., 1995; Soros, Teismann, Manemann, & Lutkenhoner, 2009), whilst 'gating out', as reflected by P50 habituation, reduces (Amenedo & Diaz, 1998; Patterson, et al., 2008), both of which may result from reduced cholinergic inhibitory activity (Pekkonen, et al., 2001; Pekkonen, Jaaskelainen, Kaakkola, & Ahveninen, 2005).

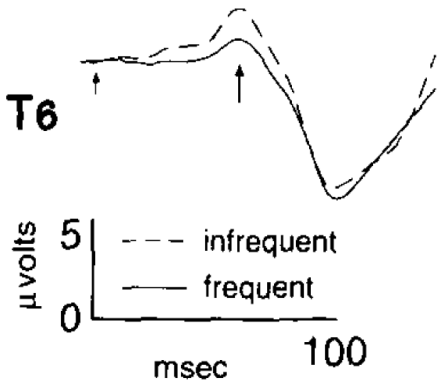


Figure 1.8: Sensory 'gating-in'
P50 response magnitude was enhanced for infrequent pitch deviants relative to frequent stimuli (c.f. Boutros, et al., 1995). Shown at right posterior temporal electrode T6.

P50 suppression is additionally *reduced* in pAD (Jessen, et al., 2001) and follows a trajectory of decline such that suppression is greatest in the young, reduced with age and furthermore with disease severity (i.e. young, elderly, MCI, pAD; (Golob, Miranda, Johnson, & Starr, 2001). The *basic P50* magnitude and latency were *increased* in individuals with MCI for both standards and infrequent target stimuli (Golob, Johnson, & Starr, 2002) and regardless of stimulus rate (so did not reflect altered refractory periods). The P50 differences were not accounted for by altered auditory brain stem responses, suggesting a cortical origin for an enhanced underlying slow wave component (Irimajiri, Golob, & Starr, 2005). The magnitude of the P50 increase in MCI participants (relative to controls) was predictive of subsequent conversion to dementia (Golob, et al., 2007).

1.4.3 Summary of spoken word MMN(m) and P50(m) in pAD

The P50(m) and MMN(m) are pre-attentive neurophysiological responses reflecting gating of auditory stimuli and short-term sensory memory, respectively, and the P50(m) in particular has been shown to be altered by Alzheimer's disease. The use of linguistic stimuli additionally enables long-term lexical/semantic neural memory traces to be probed, which may be degraded early in the course of AD. We developed an MEG paradigm to simultaneously address these different aspects of pre-attentive auditory brain responses in a patient-friendly, task-free fashion. The application of this paradigm in attempting to predict incipient dementia is described in chapters 6-9.

1.5 Thesis approach

This thesis describes the application of two MEG paradigms, an active memory paradigm investigating the memory effects described in section 1.3, and a modified passive oddball paradigm exploring the pre-attentive components described in section 1.4 within a linguistic context, to diagnosis of incipient dementia. Given the necessity of further assumptions and parameter setting in order to solve the inverse problem, and not least the greater practicality of sensor-level than source-level analyses in a clinical setting (particularly given the requirement of an MRI scan), analyses are conducted in sensor space. Although it is valid to use a template head model in young healthy individuals, this requires the assumption that there are no systematic differences in the gross shape of the cortex/scalp/skull between groups or individuals. Atrophic cerebral changes are a characteristic of both older age (Hedden & Gabrieli, 2004; Salat, et al., 2004) and AD pathology (Karas, et al., 2004; Scheltens, et al., 2002) as noted in section 1.1, thus the use of a template head model is invalid within these groups. Source localisation would therefore necessitate acquisition of a structural MRI for each individual, in addition to their undergoing the MEG procedure. Even without source localisation, in sensor space MEG offers greater ability to infer likely cortical sources compared to EEG (assuming no systematic difference between individuals in their head position within the MEG device, a possibility which we overcame using sensor-level methods). Reasons for this, as detailed in section 1.2.3, include lack of reference-dependency and freedom from 'smearing' of activity by skull and scalp, and in particular that greatest signal magnitude in planar gradiometers is detected immediately above the source of an effect. Importantly, MEG also confers the advantage of greater patient comfort as there is no requirement to endure scalp preparation and the lengthy application of numerous electrodes.

Chapters 2-5 cover the active paradigm, whilst the passive paradigm is covered in chapters 6-9. The purpose of chapter 2 was to replicate, within a group of young controls, the MEG correlates of the ERP effects previously reported in the active paradigm reviewed in section 1.3 above (further validated by concurrent recording of EEG in the same participants). The purpose of chapter 6 was two-fold; in addition to replicating passive ERP and ERF effects reviewed in section 1.4 above in young controls, we also aimed to identify novel effects of linguistic variables not explored in previous studies. The purpose of chapters 3 and 7 was to examine the effect of healthy ageing on these MEG effects, using a second group of older participants, whose ages matched those of the patients tested in subsequent chapters. A specific goal here was to establish time-windows

and sensors of interest (spatio-temporal regions of interest – ROIs) in which effects of interest within each paradigm were maximal, in order to focus on these in the patients. Chapters 4 and 8 focus on comparisons between patients diagnosed with pAD and these age-matched controls, with the aim of indentifying those contrasts that are most sensitive to dementia and constructing classification models that may be useful in detecting prodromal (MCI) stages of dementia. Finally, chapters 5 and 9 examine these contrasts in a group of patients referred from a memory clinic, who may fall into MCI or WW sub-groups; specifically we attempted to see how findings differed from those of controls and pAD patients and, despite the absence of definitive diagnoses at this stage, we assessed whether our classification models could predict a clinician's provisional diagnoses and/or add discriminatory information above that already available from neuropsychological tests.

Chapter 2
Active memory paradigm in healthy young individuals

This first experimental chapter applied the EEG paradigm used by Olichney and colleagues (2000; 2002; 2006) to a group of healthy young individuals. Both MEG and EEG were acquired concurrently, with the aim of reproducing prior ERP effects of congruency and repetition, and then comparing these with their ERF counterparts in MEG. Furthermore, we aimed to establish relationship of these ERP/ERF effects across participants to their subsequent recall performance.

In brief, the paradigm used a 2x2 design that crossed the factors of congruency (between an auditory sentence stem and subsequent visual word) and repetition (with each trial being repeated after 0-3 intervening trials). The main effects of interest), following from findings in the EEG literature, were:

1. *'Congruency Effect'* - Incongruent Initial minus Congruent Initial trials: to isolate the N400(m) component believed to relate to semantic memory (Halgren, et al., 2002; Kutas & Federmeier, 2000).
2. *'Incongruent Repetition Effect'* – Initial minus Repeat Incongruent trials: to identify attenuation of the N400(m), associated with implicit memory processes (Fernandez, et al., 2001; Finnigan, Humphreys, Dennis, & Geffen, 2002; Olichney, et al., 2000).
3. *'Congruent Repetition Effect'* – Initial minus Repeat Congruent trials: to isolate the P600(m), believed to relate to episodic memory (Finnigan, et al., 2002; Olichney, et al., 2000; Taylor & Olichney, 2007).

Aims & Predictions

Aim 1. Delineate M/EEG correlates of effects of interest

To confirm the presence of MEG counterparts to the EEG effects identified in previous work for our contrasts of interest, MEG and EEG data were acquired simultaneously. This provided opportunity to verify, via comparison with EEG data, that absence of any anticipated MEG effect or presence of novel effects in MEG data were due to differential sensitivities of the two modalities (see Chapter 1). We anticipated that given the multiple generators identified as contributing to N400 and P600 components (Halgren, et al., 1994a; Halgren, et al., 1994b; McCarthy, et al., 1995), tangentially orientated sources

would be present, rendering both visible to MEG. N400m components have been described in MEG before, but not their modulation by repetition (Halgren, et al., 2002).

Given different spatial characteristics of MEG and EEG, we expected topographical differences to be evident between these modalities, with MEG effects being more focal than those observed in EEG due to the reduced susceptibility of MEG to volume currents and distorting effects of skull and scalp boundaries (see Chapter 1). For example, MEG source solutions and studies of patients with temporal lobe epilepsy identify primarily left hemispheric sources (Halgren, et al., 1994b; Halgren, et al., 2002; Olichney, Riggins, et al., 2002), whereas the scalp N400 in EEG tends to be maximal over the right hemisphere. This is likely due to it being a far-field potential, that is, the particular orientation of the underlying source dipole produces volume currents that have maximal scalp projection at a distal site. As planar gradiometers detect greatest signal at the location immediately above the cortical source (see Chapter 1), we expect data in these sensors to show left lateralisation for N400m effects.

Given the reference-dependency of EEG, we assessed magnitude of effects when using both a nose reference that is standard in our lab, and after re-referencing offline to the average of left and right mastoid channels, which has been more often employed in previous studies using the paradigm. It was possible that effects might be differentially enhanced, or not visible, when employing either type of reference.

Aim 2. Examine relationships of M/EEG effects with recall performance

Previous studies employing the current paradigm (Olichney, et al., 2006; Olichney, Morris, et al., 2002; Olichney, et al., 2000) found strong positive correlation of magnitude of the P600 congruent repetition effect (measured by mean voltage over one or more electrodes) with free and cued recall of test items, and with neuropsychological measures of memory (memory subscale of Dementia Rating Scale, Logical Memory II of the Weschler Memory Scale – Revised and California Verbal Learning Test). Therefore relationships between memory performance and P600(m) congruent repetition effect in both MEG and EEG modalities were anticipated in the current study.

Although no prior studies employing this paradigm have found an unequivocal relationship between recall of presented items and N400(m) congruency or incongruent repetition effects, Iragui *et al.* (1996) found that latency measures of the N400 congruency effect were able to predict neuropsychological test scores. Although there were not strong grounds to predict a relationship with memory scores, we expected that

implicit memory processes represented by the N400(m) component might have some impact upon subsequent recall performance.

In addressing these questions, we employed two approaches. In the first, we took the average magnitude of an effect across the relevant time window, examining both a peak channel (maximising sensitivity to localised effects) and magnitude averaged across all channels (allowing more widespread effects to summate across space). This results in a single number for each participant, with the integration over time allowing for individual differences in latency. Our second approach regressed recall performance against M/EEG data at every point in time and space, using a massive univariate statistical parametric mapping approach (with corrections for multiple comparisons). This avoided imposing pre-defined time windows and topographies within which relationships might be captured, offering a compromise between selecting a single peak channel (which is likely to vary between individuals) and averaging across all channels (which is likely to 'water-down' relationships by including channels where the effect of interest was not present).

Aim 3. Ascertain modulation by stimulus lag of M/EEG repetition effects

Finally, we also explored the effect of repetition lag (from 0 versus 1-3 intervening trials). The small range of lags used here functioned to minimise decrements in N400 and P600 repetition effects that occur with longer delays, perhaps reflecting decay of traces in episodic memory (Olichney, et al., 2000). Nonetheless, other studies using visual item repetition in lists (e.g. Henson et al., 2004) also identified reduction in the magnitude of an earlier repetition effect at 200-300ms latency for repetitions after a single intervening item (lag 1) relative to those where no intervening items occurred (lag 0), despite an equivalent time interval of 4s between initial and repeat presentations, suggesting an additional role for interference in sensory memory. This was particularly relevant because we also found a fourth effect of interest – a relatively early main effect of repetition, particularly in the MEG, that appeared insensitive to congruency. By testing its sensitivity to immediate versus delayed repetition lags, we hoped to elucidate whether it reflected such sensory memory, as opposed to, for example, longer-lasting perceptual priming.

2.1 Method

2.1.1 Participants

Twenty-one right-handed native English speakers with a mean age of 27.9years (range = 19-38 years, SD=5.79 years), who reported no neurological or psychiatric history, were either recruited from the MRC Cognition & Brain Sciences Unit volunteer panel, or were relatives of colleagues or other participants. All gave written informed consent and were paid for their participation.

2.1.2 Design

Using MEG with concurrent EEG, we replicated a cross-modal category-word repetition paradigm (Olichney, et al., 2006; Olichney, Morris, et al., 2002; Olichney, et al., 2000), whereby participants were required to indicate whether an auditory category phrase (e.g. "a type of wood") followed by a visual word target were semantically congruent (e.g. "cedar") or incongruent (e.g. "porridge") with one another. Each auditory-phrase/visual-word trial repeated once after 0-3 intervening trials (a time interval of approximately 5 – 28s). This resulted in 4 conditions, conforming to a 2x2 factorial design of Congruent/Incongruent x Initial/Repeat. There were 108 trials for each of the 4 conditions: congruent initial, incongruent initial, congruent repeat and incongruent repeat, which were divided into 6 sessions of 72 trials (with each condition represented equally within each session). After the MEG task, participants completed an unexpected five minutes of free recall of the visual words presented during the MEG task, followed by a cued-recall test, where they were given a subset of the auditory sentence stems and asked to recall the associated visual words from before.

2.1.3 Stimuli

Two sets of 216 paired auditory category phrase-visual word stimuli were adapted from a list of category-word pairs used by Olichney *et al.* (2000). Some words were adapted from American to British English. Furthermore, a new set of congruent exemplars was generated for categories that were originally paired with incongruent word items and a new set of incongruent items was created by pairing originally congruent exemplars with the new category phrases. This was in order to counterbalance words across conditions (over subjects).

Furthermore, to match words across conditions within subjects, the suitability of the two sets of congruent words (original and new) was assessed by a pilot study on 15

native British English speakers. These pilot subjects ranked each word for typicality as a category member and for imageability, on a 5-point scale. Mean pilot ratings were moderate to high for both characteristics and did not differ across sets for either typicality (*t(14)=1.36, p>.17*) or imageability (*t(14)=1.23, p>.21*).

Word frequencies were obtained from the British National Corpus (BNC). For homographs, total BNC word frequency was multiplied by the proportion of instances out of a sample of 50 instantiating the intended meaning, to give an approximation of word frequency for that particular meaning. Words were matched across congruent and incongruent items for orthographic word frequency (*t(214)=0.109, p>.91*) and word length (*t(214)=0.531, p>.59*), whilst the auditory category phrases were matched across congruent and incongruent conditions for duration (*t(214)=0.427, p=.67*), fundamental frequency (f_0) (*t(214)=-0.687, p>.49*), and average RMS power (*t(214) =0.056, p>.95*). Stimuli are listed in *Appendix 1*.

2.1.4 Procedure

2.1.4.1 Participant preparation

Participants underwent preparation for EEG and head digitisation, prior to MEG recording. 70 silver/silver chloride EEG electrodes were positioned over the scalp, approximating the 10-10 placement system, together with a reference electrode on the tip of the nose and ground on the cheek. A mildly abrasive skin preparation gel was used and impedances were kept below 10kΩ. Participants were briefly exposed to auditory and visual stimuli, in order to confirm ability to clearly perceive both. Visual impairment was corrected with non-magnetic lenses.

2.1.4.2 MEG task

Each trial of the MEG task proceeded as illustrated in *Figure 2.1*, with an auditory category phrase preceding a visual word. Visual words in white typeface on black background were projected onto a screen. Stimulus presentation and post-MEG cued recall testing were achieved using E-prime software. The task was unspeeded and participants were instructed to wait until a prompt before responding with a button press. Participants used either the left or right index finger to indicate ‘yes’ or ‘no’ to the visually-presented question ‘Did the word match the phrase?’. Response-hand mappings were counterbalanced across participants, but remained constant within each participant.

Duration of each block was approximately 6.5 to 7.5 minutes, dependent upon response speeds. The six task-blocks were counterbalanced for order across participants.

After the MEG task, participants relaxed with their eyes closed, but not sleeping, for a further 10 minutes (these resting data are not reported in this thesis). The EEG cap and EOG electrodes were then removed and recall tasks were undertaken.

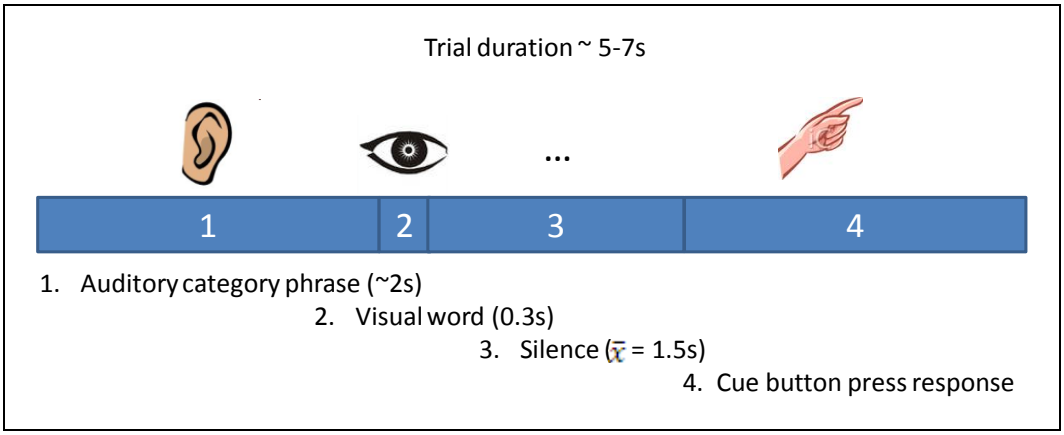


Figure 2.1: Composition and timing of a single trial during the MEG task

2.1.4.3 Recall tests

Free-recall involved recording participants' verbal responses for 5 minutes, under the instruction to verbally recall as many of the visual words that had appeared on the screen during the MEG task as possible. Cued-recall was performed subsequent to the free-recall task; participants listened via headphones to a subset of 48 category phrases from the MEG task, after each item they were asked to use a computer keyboard to type the word they believed had followed the phrase in the MEG task. Items were taken pseudo-randomly from across all blocks and comprised 50% congruent items. Participants were not under any instructions to respond as quickly as possible, therefore only accuracy was assessed.

2.1.5 MEG data acquisition

MEG data were acquired with a 306 channel (102 magnetometers / 204 planar gradiometers) VectorView MEG device (Elekta Neuromag, Helsinki), at a sampling rate of 1000Hz. HPI coil and electrode locations and head shape were digitised with Isotrak hardware and Neuromag software. Head position was continuously monitored and subsequently corrected for with Maxfilter (Elekta Neuromag, Helsinki) software. Participants' responses were recorded using a button for each index finger from bi-manual fibre-optic response boxes.

2.1.6 Data pre-processing

MEG data were processed using Maxfilter to remove activity appearing to arise from sources external to the head, via a spatiotemporal signal space separation technique 'tSSS' (Taulu & Kajola, 2005). This software was also used to interpolate values of 'bad' channels (identified via visual inspection) and to compensate for head movement during the recording. Maxfilter was run a 2nd time to realign all data such that the head origin (centre of the sphere defined via digitisation of headshape) was in an identical position for all participants, relative to the device coordinate frame.

EEGlab independent components analysis (ICA) software (Delorme & Makeig, 2004) was used for both MEG and EEG data to identify and remove components that strongly correlated with VEOG or that had the topography and appearance of cardiac artefact. Subsequent pre-processing employed SPM5 (FIL, London). A low-pass filter threshold of 44Hz was applied to the data, before epoching from -100 to 800ms relative to the onset of the visual word, and baseline-correcting from -100 to 0ms. Epochs in which sensor values surpassed a threshold (5000fT in magnetometers, 84000fT/m in planar gradiometers and 300μV in EEG) were rejected, before averaging over epochs for each condition. Although recorded relative to a nose reference, the EEG data were also transformed to a bilateral mastoid reference, for direct comparability with previous work, and to evaluate the impact of a nose reference upon inferences that can be drawn from this particular EEG data set.

2.1.7 Analyses

2.1.7.1 Signal to Noise Ratio (SNR)

SNR was based upon the mean global field power (GFP), that is, the mean of the squared signal from all sensors of a given type. SNR was calculated for each individual by averaging together GFP of all trial types, and dividing the standard deviation across the time window of the P100 visual evoked response (50-150ms) by the standard deviation across the baseline period of -100-0ms. Non-parametric tests (Wilcoxon signed ranks) were used to compare SNR across sensor types. It should be noted though that this SNR estimate is not a pure indication of noise, since it only applies to the initial P100(m) response to visual stimulation, which also might differ in true signal strength across individuals (or groups).

2.1.7.2 Identification of effects

Time windows of interest for effects of repetition and congruency were identified *a priori* from work of Olichney & colleagues and via inspection of 3-dimensional sensor x time statistical parametric maps (SPMs) (Henson, Mouchlianitis, Matthews, & Kouider, 2008). Using SPM5 (http:/www.fil.ion.ucl.ac.uk/spm), data were averaged according to condition and split into sensor modalities. For the purposes of statistical comparison, root mean squared (RMS) values were calculated for planar gradiometer pairs at each spatial location, giving a scalar value representing signal magnitude at that location. For each MEG sensor-type and the nose-referenced EEG, 3D (2Dsensor x 1Dtime) images were computed for each participant's trial-averaged data in each condition. These images for each subject were entered into a single General Linear Model (GLM) containing regressors for the 4 conditions, plus separate regressor for each participant (to remove between-participant variance of no interest). Nonsphericity in the error was estimated using Restricted Maximum Likelihood (Friston, et al., 2002). SPMs for T-contrasts corresponding to the effects of interest (see Intro) were corrected for multiple comparisons across space and time using random field theory (Worsley, 2005). For the gradiometer RMS map, the correction was based on spatial extent, using an initial height threshold of $p<.001$ uncorrected. For the Magnetometer and EEG maps, the correction was for the statistic height, because the dipolar field patterns in both cases meant that correction for extent was less appropriate (given that the same single source would produce two, non-contiguous clusters of opposite polarity). Given that both tails of the T-distribution were tested, the corrected p-values were set to $p<.025$. Sensors detecting maximal effects were located within group-average topographies and more conventional time-courses are plotted to illustrate these effects.

2.1.7.3 Laterality

The laterality of effects across sensors that were sensitive to superficial sources (i.e. gradiometers and EEG) was assessed by computing a laterality quotient (LQ) for each individual. The LQ is the ratio of the difference in field power (i.e. RMS across sensors over a hemisphere) between hemispheres divided by the sum of field power in the 2 hemispheres (i.e. L-R/L+R). Having established no significant deviation from normality in the LQ distribution across participants, these LQ data were then subjected to t-tests to measure significant deviation from zero (i.e. no laterality).

2.1.7.4 Fractional area latency (FAL)

Fractional area latency (FAL) is the latency at which the area under the curve of an effect during a pre-defined time window reaches 50% of maximum. Given the suggestion of novel and potentially temporally distinct early main effects of repetition in MEG and EEG data, FAL was computed at the sensor identified as showing maximal early repetition effect magnitude for each sensor type, across the time window of 150-400ms, which incorporated the effects evident in both MEG and EEG. T-tests were used to detect significant differences in FAL between sensor types.

2.1.7.5 Sub-analysis of repetition effects according to lag

In order to establish whether any effects of repetition were driven by visual iconic memory priming arising from immediate item repetition, an additional set of 3D (2Dsensor x 1Dtime) images and SPMs were created using a 2 (congruent/incongruent) x 5 (initial/lag0/lag1/lag2/lag3) design matrix. Given that the greatest effect of repetition due to such a process might be expected with zero intervening items, we tested this effect of lag by contrasting "Immediate Repeats" (lag 0, 25% of Repeat trials) against "Delayed Repeats" with at least one intervening item (lags 1-3, 75% of Repeat trials). Given the differing number of trials in these conditions, the contrast was weighted accordingly.

2.1.7.6 Relations of M/EEG effects with behaviour

2.1.7.6.1 Correlational analyses

The global root mean square (gRMS) field power (the square root of the mean over channels of the squared signal from *every channel* of a given type), and the magnitude for a single sensor showing the maximal effect, were averaged over all samples within the relevant time window for each effect of interest. These values were correlated with behavioural (cued- and free-recall) performance. Correction for multiple comparisons was applied to account for each effect being compared twice (single channel and gRMS measures) on two behavioural measures (cued and free recall), such that alpha for corrected significance was .05/4 = .0125. Further correction was not made for the three sensor types, as we wished to compare sensitivity across sensor types, nor was it made across effects of interest, as wished to determine and compare relationships with recall separately for each effect. This approach was somewhat more stringent than that applied in the extent literature, where correction for multiple comparisons has not typically been applied (e.g.Olichney, et al., 2006; Olichney, et al., 2000).

2.1.7.6.2 Statistical parametric regression

3D (2Dsensor x 1Dtime) images were also calculated for linear contrasts of the conditions for each particpant, corresponding to each of the three planned contrasts of interest, for each MEG sensor modality and for nose-referenced EEG. For each type of recall (cued or free), these contrast images were entered into a single GLM, which included two regressors for each of the 3 effects of interest: the mean-corrected recall score and a constant term. F-tests on each of the recall regressors were then used to identify where in time and space behavioural score was a significant predictor of recorded activity for each contrast. Regions in time and space that correlated with the main of repetition effect were identified by an average of the Congruent and Incongruent Repetition contrasts. Contrast estimates were examined for regions of significance to ascertain the direction of the relationship. Small volume correction was subsequently applied, restricting search areas to the time windows identified by the M/EEG effects described above.

2.2 Results

2.2.1 Behavioural data

Performance on the MEG congruency task was close to ceiling, as anticipated ($\bar{x}$=98.47%, SD = 1.60% correct). Cued recall for incongruent items was close to floor ($\bar{x}$=2.2%, SD = 3.39% correct), whereas performance for congruent items was higher and more variable, with a tendency towards ceiling ($\bar{x}$=80.8%, SD=11.14%). The combined (congruent & incongruent) 'cued-total' score was normally distributed, with reasonable inter-individual variability ($\bar{x}$=41.47%, SD = 6.25%), *Figure 2.2a*. This 'total cued-recall' measure was employed for further comparisons with neurophysiological data. Free recall was performed by 17 of 21 participants. Scores for total number of correct items recalled were normally distributed ($\bar{x}$=16.9, SD = 7.55)), *Figure 2.2b*. Scores for cued and free recall tests were positively correlated (r=.485, p=.024).

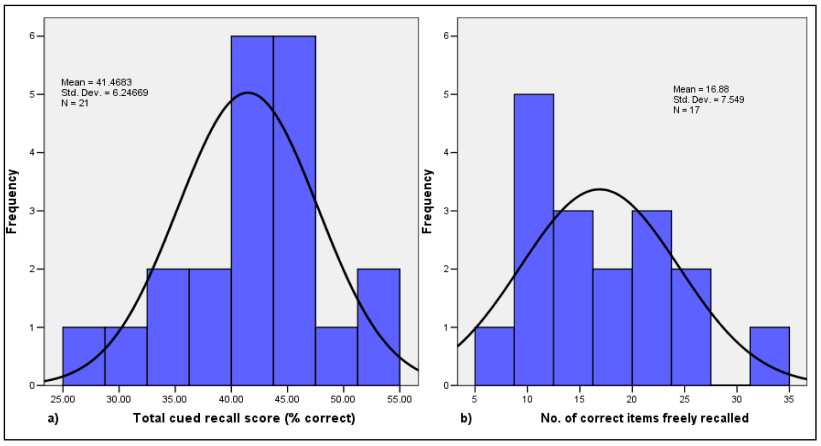


Figure 2.2: Post-MEG recall performance for test-items
a) free-recall, b) cued-recall

2.2.2 Signal-to-noise ratio (SNR)

MEG data demonstrated consistently high SNR, with mean values of 22.6 (10.59) and 26.3 (14.89) for magnetometers and gradiometers respectively. Gradiometers had higher SNR than magnetometers (Wilcoxon signed ranks: Z=-2.033, p=.042). One participant's gradiometer data were excluded from further analyses as the standard deviation during both baseline and signal time windows was an order of magnitude greater than for any other participant.

EEG data for two participants were excluded from further analyses, due to SNR below 1.5. Remaining EEG data had minimum SNR of 2.66 and a mean of 12.5 (13.44), significantly lower than for MEG data (Wilcoxon signed ranks: EEG-magnetometers: Z=-3.099, p=.002; EEG-gradiometers: Z=-3.582, p<.001).

2.2.3 N400(m) congruency effect

The effect of congruency upon initial presentation of items was significant in the sensor SPM for nose-referenced EEG from 350-530ms. The group topography and time course at electrode P4 confirmed greater negative amplitude for incongruent trials, with similar effect magnitude when data were re-referenced to bilateral mastoids (see *Figure 2.3*). The N400m congruency effect in MEG data extended for a similar time period in both sensor types, in gradiometers the effect was emphasised over left temporal sensors.

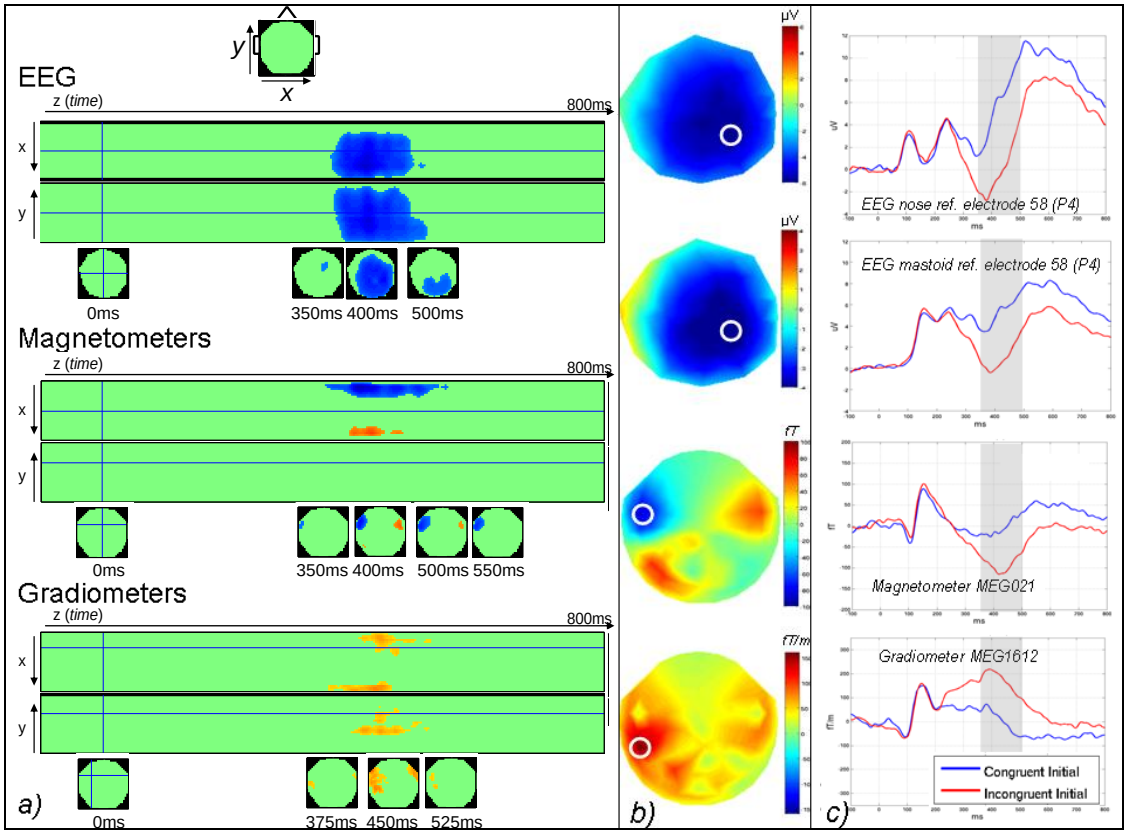


Figure 2.3: N400(m) congruency effect

a) 3D sensor x time SPM for two-tailed T-test, thresholded for height @ p=.05 (FWE-corrected) for nose-referenced EEG and magnetometers, thresholded for height @ p=.001(uncorrected) & extent @ p<.05 (FWE-corrected) for gradiometers; b) Group average topography at 350-500ms, from top to bottom: nose-referenced EEG, mastoid-referenced EEG, Magnetometers, Gradiometers; c) Time course at peak sensor (location circled in b), order as for b.

Lateralisation across the 350-500ms time window was right-sided in both mastoid- and nose-referenced EEG (*Mastoid-referenced: t(19)=-2.28, p=.035; Nose-referenced: t(19)=-2.32, p=.033*), in accordance with existing literature, whilst there was strong left lateralisation in gradiometers (*t(19)=4.53, p<.001*).

2.2.4 N400(m) incongruent repetition effect

For EEG, a reduction of the N400 response to incongruent items occurred when they were repeated, with slightly earlier onset and more widespread spatial distribution, but reduced magnitude than the congruency effect for nose-referenced data. This repetition effect was of lesser magnitude and duration when re-referenced to bilateral mastoids (*Figure 2.4*).

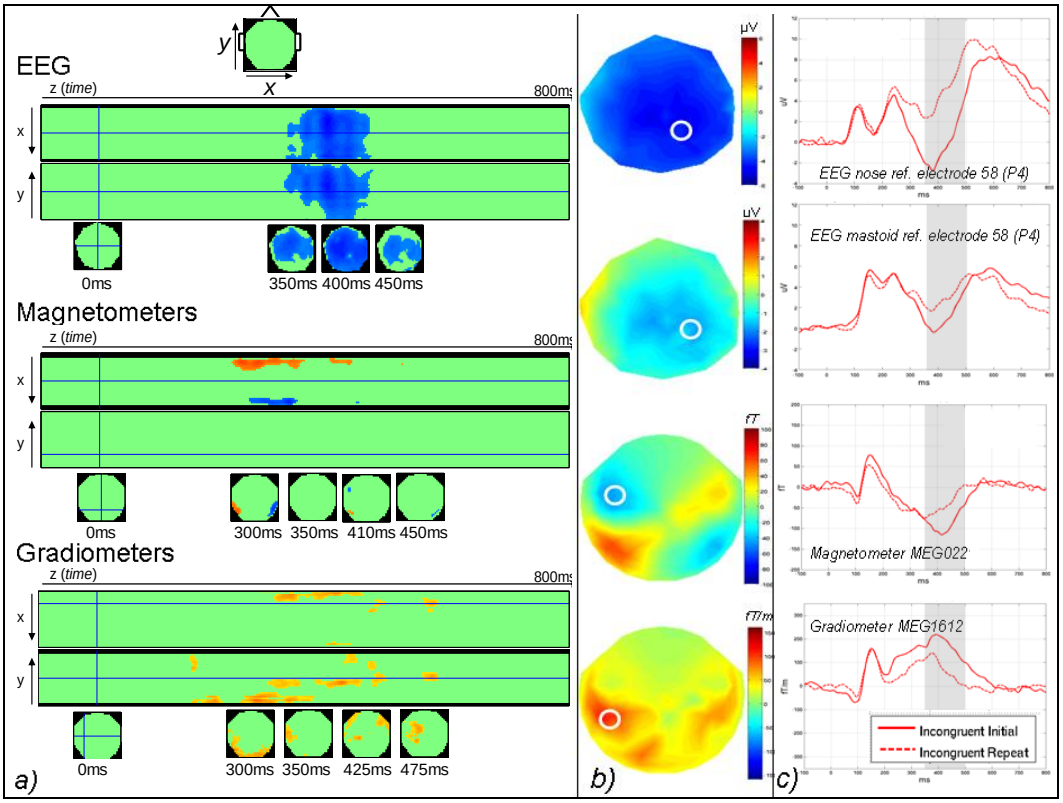


Figure 2.4: N400(m) incongruent repetition effect

a) 3D sensor x time SPM for two-tailed T-test, thresholded for height @ p=.05 (FWE-corrected) for nose-referenced EEG and magnetometers, thresholded for height @ p=.001(uncorrected) & extent @ p<.05 (FWE-corrected) for gradiometers; b) Group average topography at 350-500ms, from top to bottom: nose-referenced EEG, mastoid-referenced EEG, Magnetometers, Gradiometers; c) Time course at peak sensor (location circled in b), order as for b.

Magnetometer data showed a spatially restricted attenuation of the N400m waveform upon item repetition, from around 400-450ms, whilst gradiometers (which had less stringent height thresholding) detected a repetition effect in the N400m time window that appeared predominantly left (but also right) temporal in overall emphasis. Earlier effects in sensor SPMs for the MEG modality were seen from around 150ms, they were spatially distinct in gradiometers from the N400m repetition effect, with a bilateral posterior distribution, and will be discussed later.

As observed for the congruency effect, there was potent left-lateralisation in gradiometers (*t(19)=3.75, p=.001*) and a trend towards right lateralisation in mastoid-referenced EEG (*t(19)=-1.73, p=.051,one-tailed*) for the N400(m) repetition effect. No significant lateralisation was evident when EEG data were referenced to the nose (*t(19)=-0.934, p>.35, one-tailed*).

2.2.5 P600(m) congruent repetition effect

Replicating earlier findings, the P600 ERP component was reduced upon repetition of congruent items, which we found whether referenced to nose or bilateral mastoids. The same attenuation was found in magnetometer data, from approximately 600-800ms, and with a left posterior emphasis in gradiometer data between 500-700ms; see *Figure 2.5*.

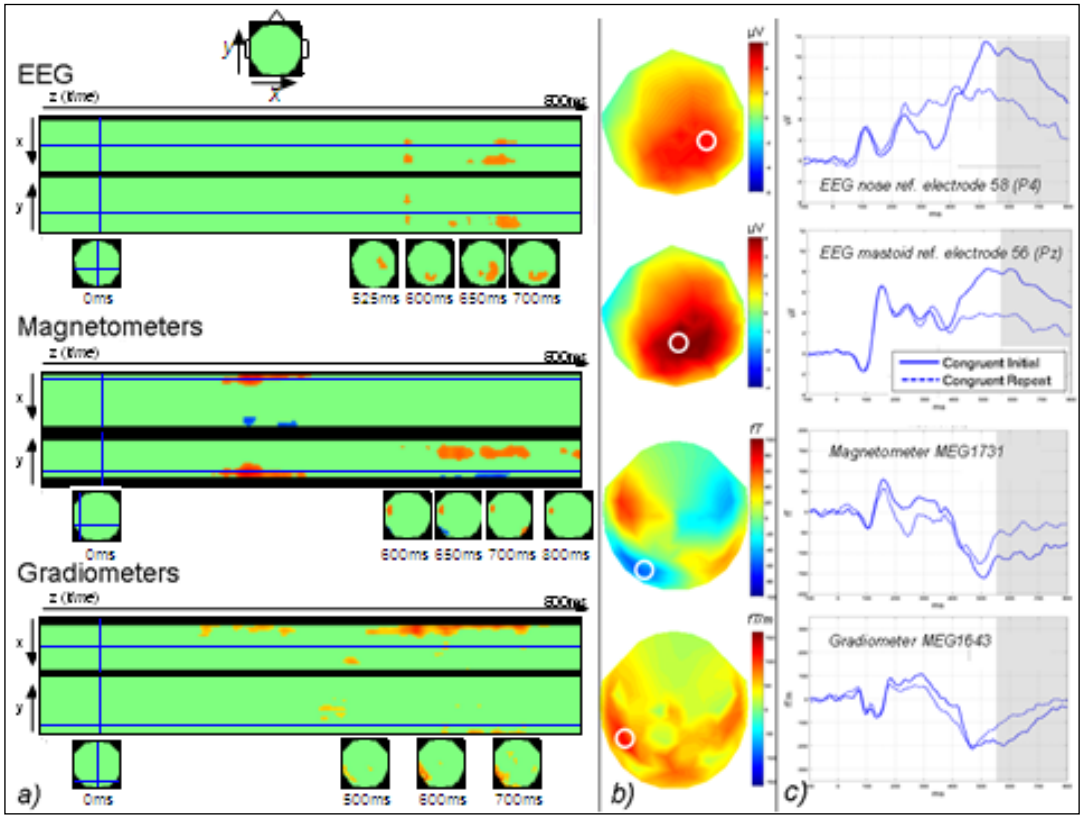


Figure 2.5: P600(m) congruent repetition effect

a) 3D sensor x time SPM for two-tailed T-test, thresholded for height @ p=.05 (FWE-corrected) for nose-referenced EEG and magnetometers, thresholded for height @ p=.001(uncorrected) & extent @ p<.05 (FWE-corrected) for gradiometers; b) Group average topography at 550-800ms, from top to bottom: nose-referenced EEG, mastoid-referenced EEG, Magnetometers, Gradiometers; c) Time course at peak sensor (location circled in b), order as for b.

Earlier effects of repetition, from approximately 250-400ms in the EEG (evident only when using a nose reference), and even earlier from 140-350ms in the magnetometers, had different polarity to the P/600m repetition effect, suggesting different generators, and are considered in more detail in the next section.

The P600(m) effect was significantly right-lateralised in EEG referenced to bilateral mastoids ($t(19)=-2.41$, $p=.027$) but not in nose-referenced EEG ($t(19)=-0.844$, $p>.4$) nor was there significant laterality of the effect in gradiometers, despite the suggestion of left-sided emphasis in the sensor SPM ($t(19)=1.39$, $p>.17$).

2.2.6 Early main effect of repetition

The MEG data revealed a main effect of repetition that did not show any reliable interactions with congruency (before 400ms). Magnetometers depicted a pattern of activation throughout 150-350ms, whilst gradiometers displayed a persistent effect with left posterior emphasis during a similar temporal window with subsequent ongoing effect having a distribution similar to that of the N400m repetition effect (see *Figure 2.6*).

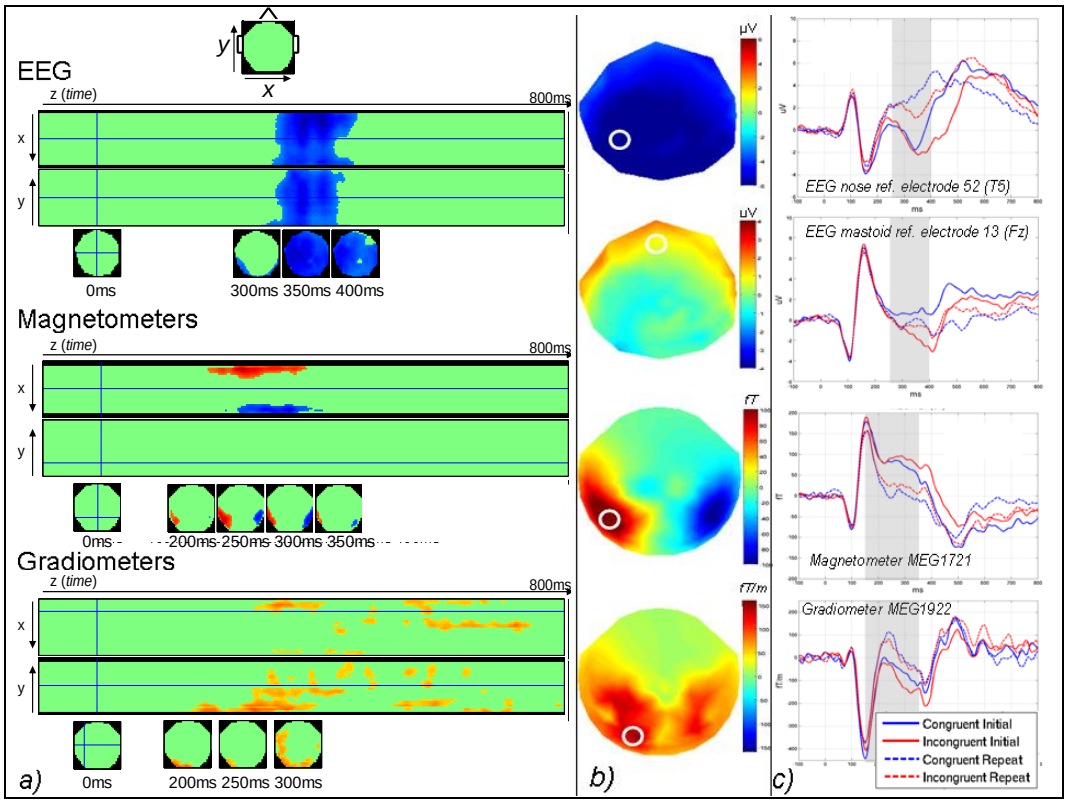


Figure 2.6 Early main repetition effect

a) 3D sensor x time SPM for two-tailed T-test, thresholded for height @ p=.05 (FWE-corrected) for nose-referenced EEG and magnetometers, thresholded for height @ p=.001(uncorrected) & extent @ p<.05 (FWE-corrected) for gradiometers; b) Group average topography: 250-400ms in EEG; 150-350ms in MEG; from top to bottom: nose-referenced EEG, mastoid-referenced EEG, Magnetometers, Gradiometers; c) Time course at peak sensor (location circled in b), order as b.

Nose-referenced EEG data also showed an early repetition effect, which emerged at 280ms in left-posterior channels and persisted until around 450ms, as with MEG data there was no significant interaction with congruency until 400ms. However, this effect was not apparent when EEG was re-referenced to mastoid electrodes, instead polarity of early differences varied according to congruency, reflecting onset of P600/N400 repetition effects, rather than the distinct earlier process evident with a nose reference.

The effect in gradiometers was left-lateralised ($t(19)=2.37$, $p=.028$) in the 150-350ms time window. There was no significant lateralisation from 250-400ms in nose-referenced EEG ($t(19)=-0.377$, $p>.7$).

2.2.6.1 Latency of early repetition effect

Fractional area latency (FAL) across the 150-400ms window for the early repetition effect was significantly later in nose-referenced EEG, with mean FAL of 313ms (SD=19.3ms), than both magnetometers and gradiometers, with mean FAL of 283ms (SD=10.7ms) and 284ms (SD=11.4ms) respectively (*Magnetometers-EEG: $t(19)=-5.70$, $p<.001$; Gradiometers-EEG: $t(18)=-5.94$, $p<.001$; Magnetometers-Gradiometers: $t(19)=-0.315$, $p>.7$*). This latency difference is visualised in global RMS time courses in *Figure 2.7*. An early repetition effect in the negative direction began at around 200ms for both congruent and incongruent items in nose-referenced EEG, peaking at approximately 350ms and 400ms for congruent and incongruent items respectively, whereas the first effects in MEG data appeared to begin at around 150ms and peaked around 200-250ms irrespective of item congruency. Later MEG peaks coincident with the first EEG peaks were noted.

2.2.7 Effect of repetition lag

Given possible effects of repetition lag explained in aim 3, we contrasted immediate (lag 0) with delayed (lags 1-3) repeats directly (collapsing across congruency). There were no reliable differences in magnetometers or in EEG. The gradiometers showed an immediate/delayed repeat difference between 260-300ms over right central/parietal sensors, which appeared to be driven by an immediate repetition effect for incongruent items, that was not present for delayed or immediate repetition of congruent items. Although temporally coincident with the early main effect of repetition reported above, its spatial distribution appeared distinct. We therefore decided not to explore the effect of repetition lag further; the more important finding from the present analyses was that repetition in this paradigm appeared largely unaffected by lag.

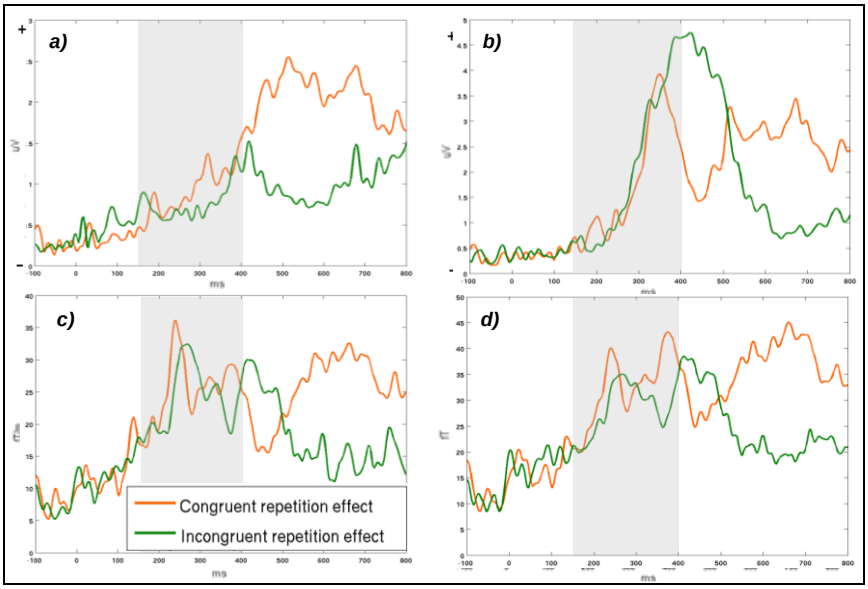


Figure 2.7: Global RMS time courses of repetition effects
a) Bilateral mastoid referenced EEG; b) Nose referenced EEG;
c) Magnetometers; d) Gradiometers.
Shaded areas indicate time window (150-400ms) used to compute FAL.

2.2.8 Relations of neurophysiology and behaviour

2.2.8.1 Correlations

Values for correlations of recall measures with magnitude of M/EEG effects of interest (averaged across time windows defined from previous literature and with reference to sensor SPMs and time courses at peak sensors) are summarised in *Table 2.1* and depicted in *Figure 2.8.* Strong positive correlations existed between global RMS of the N400m congruency effect in both MEG sensor modalities and cued recall performance, whilst in the (nose-referenced) EEG modality a near-significant trend was present for single-channel amplitude at electrode P4 with cued recall score. With regard to free recall performance, only a non-significant trend was evident for correlation with global RMS in magnetometers.

The only significant relationship (uncorrected for multiple comparisons) with the N400(m) incongruent repetition effect was for cued recall score with global RMS in magnetometers, although non-significant trends were present for global RMS in gradiometers and single-channel amplitude of EEG. Free recall score showed no significant correlation with any N400(m) repetition effect measures.

As expected, P600(m) congruent repetition effect magnitude was significantly positively correlated with cued recall performance in both MEG and EEG. The relationship was present for global RMS of MEG sensors and single-channel amplitude (electrode P4) in the EEG data, surviving Bonferroni correction for multiple comparisons

in both types of MEG sensor. No significant correlations were detected between this effect and free recall performance.

The early main effect of repetition correlated significantly positively with subsequent cued-recall of MEG task items for global RMS in both MEG sensor modalities (although only the gradiometer effect survived Bonferonni correction) and with RMS magnitude at gradiometer MEG173g, which also demonstrated a near-significant trend for correlation with number of correct items freely recalled. There were no significant correlations between the EEG effect and either recall measure.

Table 2.1: Correlations between neurophysiological effects and recall performance

Correlations		Congruency N400(m) 350-500ms		Incongruent Repetition N400(m) 350-500ms		Congruent Repetition P600(m) 550-800ms		Early Repetition MEG:150-350ms, EEG: 250-400ms **	
		RMS	Chan	RMS	Chan	RMS	Chan	RMS	Chan
Mags	Cued recall r	.582	.260	.446	-.097	.621	.298	.436	.114
	Cued recall p	.003	.128	.021	.337	.001	.094	.048	.614
	Free recall r	.380	.171	.153	.022	.227	-.052	.071	-.052
	Free recall p	.066	.256	.279	.467	.191	.421	.786	.844
Grads	Cued recall r	.567	.121	.332	.155	.587	.280	.547	.521
	Cued recall p	.004	.306	.071	.257	.003	.116	.010	.018
	Free recall r	.306	.016	.117	.271	.078	.343	-.053	.471
	Free recall p	.116	.476	.327	.147	.383	.089	.840	.056
EEG *	Cued recall r	.206	-.376	.320	-.343	-.017	.422	.248	-.126
	Cued recall p	.198	.056	.091	.075	.946	.029	.306	.608
	Free recall r	-.023	-.227	.088	-.032	-.226	.114	.416	-.021
	Free recall p	.934	.199	.373	.453	.400	.337	.110	.938

* Nose-referenced EEG data ** One-tailed tests of significance were used for all effects except the early repetition effect, for which two-tailed tests were used as there were no predictions regarding direction of relationship of this effect with recall. Grey shading = significant @ p<.05; blue shading = significant @ p<.0125.

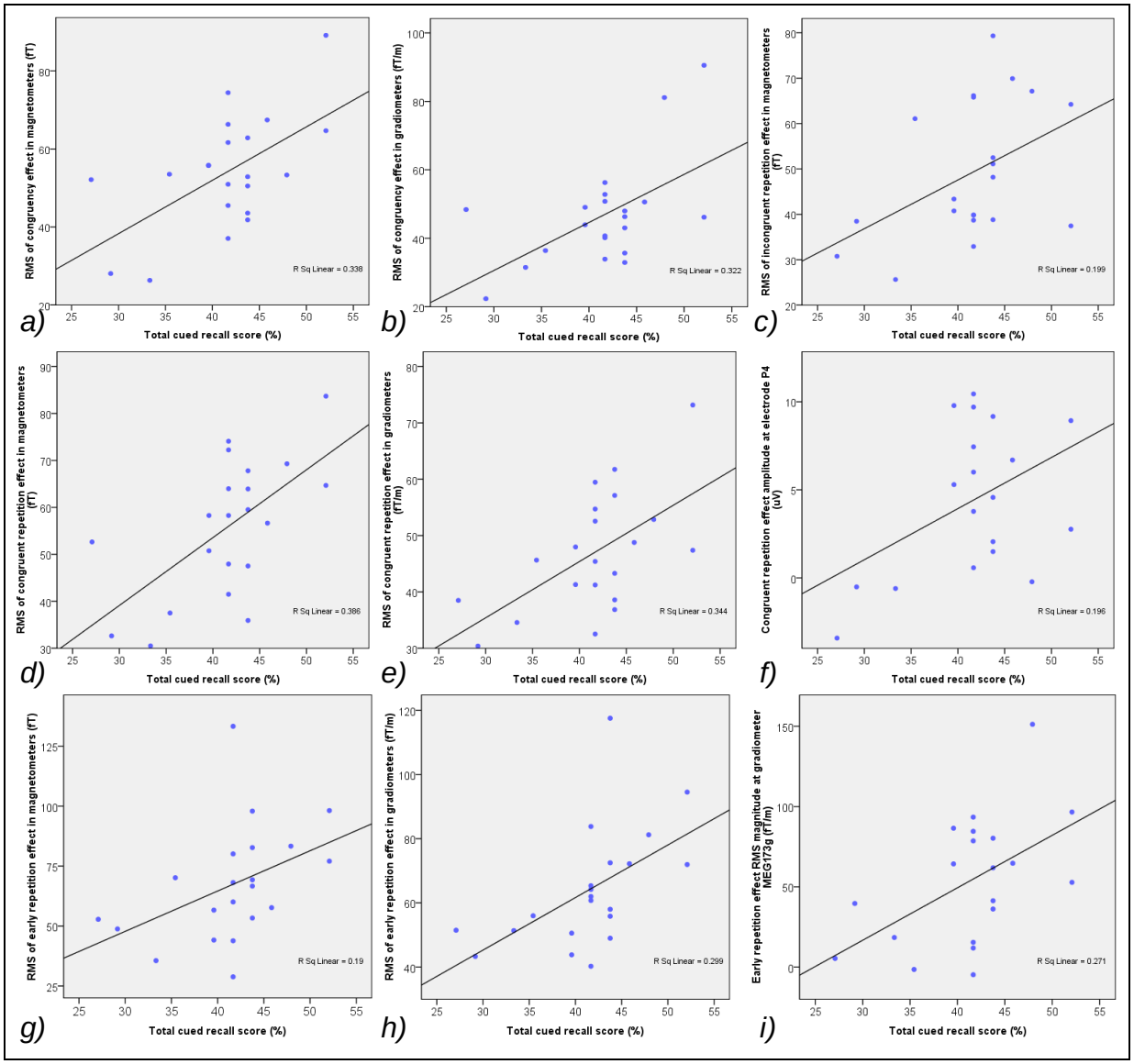


Figure 2.8: Correlations of M/EEG measures with total cued recall score
N400m congruency effect (350-500ms): global RMS in a) magnetometers & b) gradiometers; N400m incongruent repetition effect (350-500ms): c) global RMS in magnetometers; P600(m) congruent repetition effect (550-800ms): global RMS in d) magnetometers & e) gradiometers & f) amplitude at EEG electrode P4; Early repetition effect (150-350ms): global RMS in g) magnetometers & h) gradiometers & i) RMS magnitude at gradiometer MEG173g.

2.2.8.2 Regression of recall with M/EEG effects across sensors and time

In the regressions across sensor space and time, all anticipated relationships between behavioural cued recall score and M/EEG repetition contrasts were detected, as were additional relationships during the early effect time windows (150-350ms in MEG and 250-400ms in EEG). See *Figure 2.9* for a summary of results depicting SPMs for the regression of cued recall score with M/EEG contrasts. Results for the regression of free

recall score with M/EEG contrasts are not explicitly reported here, but were very similar to those for the regression of cued recall.

Cued recall score significantly related to the congruent repetition effect in EEG (*Figure 2.9c*), both during the P600 window (between 600 and 800ms, with a widespread spatial distribution) as reported in previous EEG studies, and during the early 250-400ms time window (predominantly right temporal). Likewise, a significant relationship was present between cued recall score and N400 incongruent repetition effect (*Figure 2.9*), with right anterior/temporal distribution, evident from 250ms but more distinct during the N400 (350-500ms) time window. A similar relationship of N400 congruency effect with cued recall was evident with almost identical spatial distribution but slightly later onset.

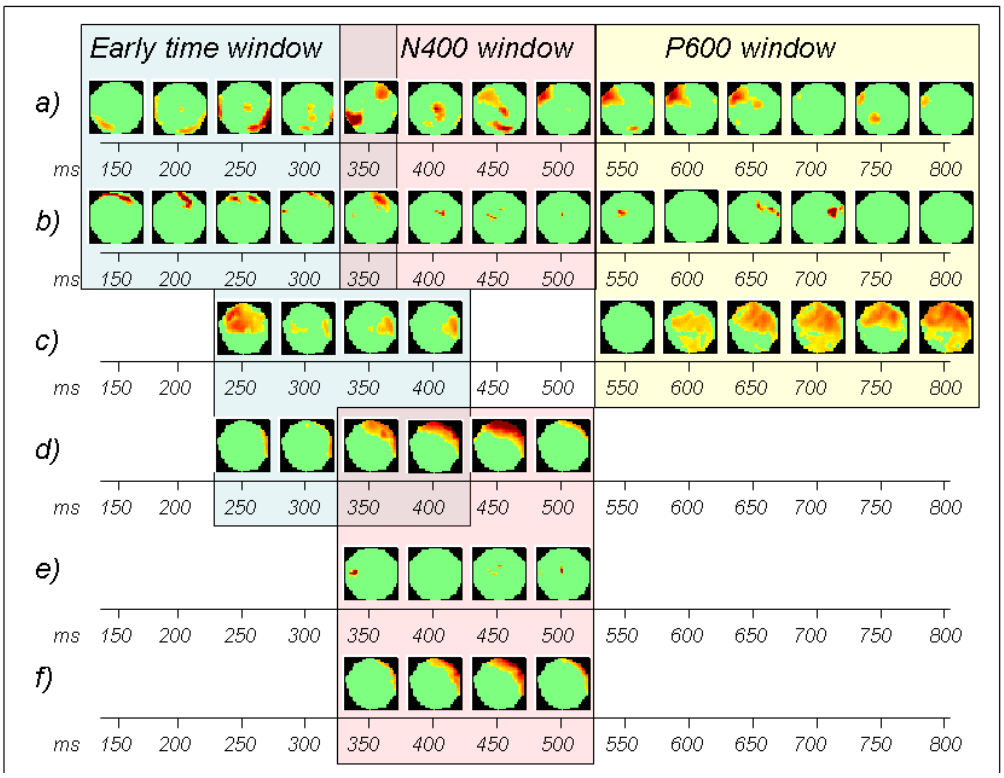


Figure 2.9: Cued recall as a significant predictor of M/EEG contrast effects
3D sensor x time regression F-test, thresholded for height @ p<.001(uncorrected) and extent @ p<.05(FWE-corrected).a) Repetition effect in magnetometers; b) Repetition effect in gradiometers (difference in RMS); c) Congruent repetition effect in nose-referenced EEG; d) Incongruent repetition effect in nose-referenced EEG; e) Congruency effect in gradiometers (difference in RMS); f) Congruency effect in nose-referenced EEG.

Examination of contrast estimates revealed that relationships with recall seen within the EEG early time window were in opposite directions for congruent (positive correlation) and incongruent (negative correlation) repetition effects, despite both effects occurring in the same (negative) direction regardless of congruency. Greater magnitude

of the effect for incongruent items was associated with enhanced memory, whereas greater magnitude for congruent items was associated with impaired recall.

Unlike in EEG, SPMs regressing cued recall with congruency effect magnitude detected very limited significant co-variation for gradiometers (*Figure 2.9e*) and no relationship for magnetometers. Significant relationships between cued recall and repetition effects were present during all time windows in both modalities of MEG sensor (*Figures 2.9a-b),* without any differential relationship according to item congruency. Indeed, all relationships with cued recall were more prominent for the combined repetition effect, as opposed to either congruent or incongruent repetition alone.

2.3 Chapter summary

In relation to our first aim, in MEG we replicated EEG effects and their MEG counterparts believed to reflect aspects of semantic and episodic memory function. We also identified a novel MEG repetition effect at an earlier latency (150-350ms) for which counterparts were not present in the EEG data. In relation to aim 2, we found that all effects bore relation to subsequent recall of items encountered during the MEG task. Finally, repetition lag was excluded as a confounding factor (aim 3).

2.3.1 Congruency N400(m) effect

A congruency effect was evident in both EEG and MEG modalities in the expected time window; lateralisation was right-sided for EEG and left-sided for MEG as predicted (aim 1). In both MEG sensor types, global RMS of the congruency effect was strongly correlated with cued recall performance, whilst a marginally significant relationship was evident at the peak channel in nose-referenced EEG.

2.3.2 Incongruent repetition N400(m) effect

Reduction of the N400(m) upon repetition of incongruent items occurred during the anticipated time window. Although of lesser magnitude, it appeared more focal in distribution for mastoid-referenced than nose-referenced data and showed a marginally significant trend for right-lateralisation. Both types of MEG sensor detected a significantly left-lateralised effect.

As reported in previous studies, no correlations were evident between the EEG effect and recall performance. The SPM regression did however reveal a relationship between cued recall and the EEG incongruent repetition effect over right frontal and

temporal regions, spatially coincident with the relationship between N400 congruency effect and cued recall, distal to the location of the electrode detecting peak effect magnitude that was used for correlational analysis. Regarding MEG, global RMS of the effect in magnetometers (but not gradiometers) was significantly positively correlated with cued recall performance (although this did not survive correction for multiple comparisons), whilst in the SPM regressions, a relationship was evident in both MEG sensor types. The strongest relationship between cued recall and N400m repetition effect occurred when repetition of both congruent and incongruent items was taken into account.

2.3.3 Congruent repetition P600(m) effect

A reduced EEG P600 component with congruent item repetition was right-lateralised and of greatest magnitude in mastoid-referenced EEG, in contrast with some (but not all) previous studies that identified a left-lateralised scalp distribution for the P600 component (Van Petten, et al., 1991). In MEG, a magnitude reduction that was not significantly lateralised occurred during a similar time window in gradiometers, whilst the effect became significant a little later (around 600ms) in more stringently thresholded magnetometer data.

Effect magnitude at the peak EEG electrode correlated positively with cued recall performance, as did global RMS of the effect in both types of MEG sensor. These relationships were also evident in the SPM regression analyses, although, as for the N400m repetition effect, the MEG relationship with recall performance was strongest when repetition of both congruent and incongruent items was considered.

2.3.4 Earlier effects of repetition

Both incongruent and congruent repetition contrasts revealed an earlier MEG effect beginning around 150ms, which was subsequently found to be congruency-indifferent. Spatial distribution was distinct from the N400m repetition effect in gradiometers although still left-lateralised, whilst polarity in magnetometers was opposite to that of the P600m repetition effect. Nose- (but not mastoid-) referenced EEG data revealed a widespread, left-lateralised main effect of repetition. This began distinctly later than the MEG effect, at approximately 250ms, in the opposite direction to the P600 repetition effect and was indifferent to congruency until 400ms.

There were positive correlations with cued recall for global RMS in both sensor types and at the maximal gradiometer channel, but not for the earliest EEG effect. SPM regressions identified relationships with cued recall for both MEG and EEG during their respective ‘early repetition effect’ time windows; however, the direction of the EEG relationship co-varied according to item congruency, such that a larger effect for incongruent items was associated with better recall performance, whereas a larger effect for congruent items tended to be associated with poorer recall performance.

Chapter 3
Active memory paradigm in healthy older individuals

Chapter 2 explored the presence and spatio-temporal distribution in a young healthy population of MEG effects believed to reflect neurophysiological components of semantic (N400m) and episodic (P600m) memory. The following chapter contrasts these findings with a group of neurologically healthy older people, who performed an identical MEG task.

Our effects of interest, following on from findings in the younger group, were:

1. *'Congruency Effect'* (*'CE'*) - Incongruent minus Congruent Initial trials to examine the N400m component believed to be linked to semantic memory (Halgren, et al., 2002; Kutas & Federmeier, 2000).
2. *'Incongruent Repetition Effect'* (*'IRE'*) – Initial minus Repeat Incongruent trials to examine N400m activity decrement, believed to be associated with priming / implicit memory processes (Fernandez, et al., 2001; Finnigan, et al., 2002; Olichney, et al., 2000).
3. *'Congruent Repetition Effect'* (*'CRE'*) – Initial minus Repeat Congruent trials to isolate P600m components associated with episodic memory processes (Finnigan, et al., 2002; Olichney, et al., 2000; Taylor & Olichney, 2007).
4. *'Main Repetition Effect'* (*'RE'*) - All Initial minus All Repeat trials, to further investigate pre-400ms congruency-indifferent reductions in MEG activity associated with item repetition.

Aims & predictions

Aim 1. Characterise any impact of age upon effects of interest.

We compared latency (FAL), absolute magnitude and topography (having adjusted for latency differences) between the younger and older age groups. Increased latency of N400 effects with age has been widely reported in the literature (Federmeier & Kutas, 2005; Kutas & Iragui, 1998) and interpreted as reflective of less efficient semantic search with age. In order to compare magnitude and topography of effects, it was therefore necessary to define time windows that capture equivalent portions of the response across both age groups.

For topographic analyses, we selected spatio-temporal regions of interest (ROIs), and used ANOVA to assess the interaction of age group with hemisphere, motivated by findings in the fMRI and PET literature (Cabeza, 2001; Dolcos, Rice, & Cabeza, 2002) which suggest that older people tend to show more bilateral activation (i.e. reduced laterality) than their younger counterparts. Likewise, where an effect was evident over both anterior (frontal/fronto-temporal) and posterior (parietal/temporal/ occipital) regions, interactions between age-group and rostrality would add support to the further hypothesis that older people show a 'posterior-to-anterior shift with ageing', that is, increased anterior and decreased posterior activation relative to younger individuals (Davis, et al., 2008).

ROIs were defined by statistical maxima identified in the initial SPM analyses, thus avoiding bias towards sensors closer to the head (where signal is largest). In order to avoid biasing the topographic analysis towards one age-group or the other, when maxima differed between groups, the above ANOVAs included an additional factor of "maxima" and ROIs defined from each group were incorporated into the analysis. Any condition effects were therefore unlikely to be biased towards either group, while any interactions with this factor would suggest smaller-scale topographic differences with age (with implications for aim 3).

Aim 2. Describe topographical properties of the contrast conditions.

Any reliable effects of laterality or rostrality in the above ANOVAs (even regardless of age-group) give some statistical evidence about the location of the underlying cortical generators (e.g. hemisphere and lobe). This is unlike the SPM analysis where no tests are done across voxels, that is, across sensor-space (or time). Effects of laterality or rostrality are most easily interpreted when detected in gradiometers, where the signal magnitude (RMS of the planar field gradient) is maximal directly above a generator. Such effects are more difficult to interpret with magnetometer data however, where the maximal signal is displaced from an underlying dipolar source (see chapter 1). Furthermore, the sign of the signal (reflecting the direction of magnetic flux in or out of the head) depends on the orientation of the source; a midline source oriented anteriorly or posteriorly would yield a positive maximum in one hemisphere and a negative maximum in the other. Putting these values directly into ANOVA would lead to an interaction with the laterality factor that did not reflect a hemispheric difference in location. To avoid the latter problem, we used

the absolute value (equivalent to RMS for a single sensor) of the magnetometer ROIs in the ANOVAs.

When exploring the RMS of gradiometer data, we found that some differences between conditions were missed when first computing the RMS for each condition and then taking the difference ('difference in RMS'), namely those that led to signals with different polarities relative to baseline. For example, the RMS of a positive deflection in one condition would not differ from the RMS of a negative deflection in another condition that was of equal magnitude. This even led to artefactual age differences for an effect of interest, when the signal for original conditions at an ROI varied between groups in when they crossed zero (see section 3.2.3.2 for an example). We therefore performed all ANOVAs on the RMS of differences between conditions, rather than on differences in the RMS of each condition. This overcame the problem of different polarities versus baseline, though the downside was that the direction of the difference in magnitude across conditions was lost. It should be noted that for the gradiometers, the results can therefore differ from the SPM results (which tested the difference in RMS for each condition, not the RMS of condition differences). Where the gradiometer results differed under these complementary approaches, it was noted.

Finally, given that anterior MEG sensors are usually more distant from cortex than those located more posteriorly in the sensor array and that the signal scales nonlinearly with distance, any effect of rostrality may simply reflect reduced signals from more distant sources. Such effects were therefore interpreted with caution.

Aim 3. Define sensors offering maximal sensitivity to effects in patients.

The final aim of this chapter was to select ROIs for comparison between the older control group and the patients considered in the next chapter. In order to maximise sensitivity to effects of incipient dementia we wanted to use the control data to select a few features of the data (i.e. sensors and time windows) where condition effects were maximal. Ideally, this selection would be independent of the older control and patient groups – for example, defined by the maxima of condition effects in the young controls. However, such a selection might be sub-optimal for a comparison between older aged individuals. Therefore, when we found no reliable difference in the maxima across young and old controls, we selected the ROIs from the young group maxima for the patient analysis in the next chapter. Where we did find age effects, on the other hand, we selected ROIs from older maxima, in order to maximise sensitivity (acknowledging potential bias in the ROI)

to any differences in the patients. Maxima for each group were selected according to maximal SNR, that is, sensor SPM peaks, whereas the ANOVAs used to contrast groups were computed using RMS of effect magnitude averaged across the time window of interest at the sensor closest to each sensor SPM maximum.

3.1 Method

3.1.1 Participants

Participants were 28 (11 male) individuals, with a mean age of 69 years (SD=5.9years, range 58-78 years), one of whom was ambidextrous and two were left-handed, the remainder were right-handed. Participants were recruited either from the CBU volunteer panel or were friends/relatives of staff/other volunteers and reported no neurological or psychiatric history. A subset of 17 participants had completed the ACE-R test battery as part of a separate study at the CBU and had given permission for that data to be used by other researchers. All scored within the normal range for age. These scores are not considered further here, but were used for comparisons with patient groups described in subsequent chapters.

3.1.2 Procedure

The MEG active memory task and procedure were identical for the older and younger groups, with the exception that in this case only 15 EEG electrodes, conforming to a reduced 10-20 montage (referenced to the nose) were applied. Given that this limited EEG coverage prevented full topographic comparison across age groups, the EEG data from the older group were only used informally, to check the basic N400/P600 effects described in the previous chapter. These effects were confirmed, and these data are not reported further here. During subsequent behavioural testing, the older group performed only cued recall, without any preceding free recall task. Pre-processing of MEG data was identical to that used for the younger group's data.

3.1.3 Analysis approach

3.1.3.1 Signal-to-noise ratio (SNR)

SNR was computed as in the previous chapter. Non-parametric tests were employed for comparisons between sensor types (Wilcoxon signed ranks) and between groups (Mann-Whitney U test).

3.1.3.2 Whole head analysis

3D sensor x time SPMs were examined to identify significant MEG effects within the older group and any age-group related differences. As explained in the preceding chapter, sensor SPMs are able to indicate both the time window and spatial distribution when significant differences occur between conditions. A sensor that was closest to the SPM maximum for each contrast of conditions in each hemisphere was selected for each group (or with a homolog from the opposite hemisphere if maxima were not bilaterally suprathreshold).

3.1.3.3 Latency and selection of time windows of interest

Excluding any magnitude deviations in the opposite direction to our effect of interest, fractional area latency (FAL) was computed on the most prominent younger group maxima for each sensor type, identified in the previous step. The time window across which FAL was computed was selected both to be comparable with windows used in prior EEG studies (Olichney, Morris, et al., 2002; Olichney, et al., 2000) and to be inclusive of periods of greatest effect magnitude evident in sensor SPMs and time courses. The windows used to compute FAL were 300-600ms for N400m effects, 550-800ms for the congruent repetition effect and 150-400ms for the early repetition effect. Histograms were consulted to provide insight into the distribution and to ascertain if means were representative of the data and T-tests were utilised to identify significant FAL differences between age groups. Where a significant latency difference existed between groups, time windows of ROIs for the ANOVAs below were adjusted accordingly (see later).

3.1.3.4 Single-channel analyses

For each sensor identified in step 1, the mean RMS of the difference between original conditions was computed across the time window determined in step 2, for each individual. This produced a single-value from each spatio-temporal ROI for each individual that was used as input for 2(age-group) x 2(maxima; where these did not coincide across groups) x 2(hemisphere) x 2(anterior/posterior; where both anterior and posterior effects were present in the SPMs) factor ANOVAs.

3.2 Results

3.2.1 Behavioural data

For the older group, as for the younger group, performance on the MEG congruency task was close to ceiling ($\bar{x}$=98.0%, SD=2.1% correct).

Cued recall scores did not significantly differ from those of the younger group (*Younger-Older: Incongruent items: t=0.75, p>.4; Congruent items: t=-0.14, p>.8; All items: t=0.10, p>.9*). See *Figure 3.1*. Cued recall for incongruent items was close to floor ($\bar{x}$=1.5%, SD=3.0% correct) and far higher for congruent items ($\bar{x}$=81.2%, SD=12.7% correct). Even though the effect of adding incongruent to congruent recall scores was small, the 'cued-total' score for cued recall of all items was the most normal in distribution ($\bar{x}$=41.3%, SD=6.1% correct).

Despite the greater range of scores in the younger compared to older cued recall data, variability in scores did not differ between groups (*Levene's Test: Incongruent: F=1.59, p>.2; Congruent: F=1.72, p=.2; All items: F=0.70, p>.4*).

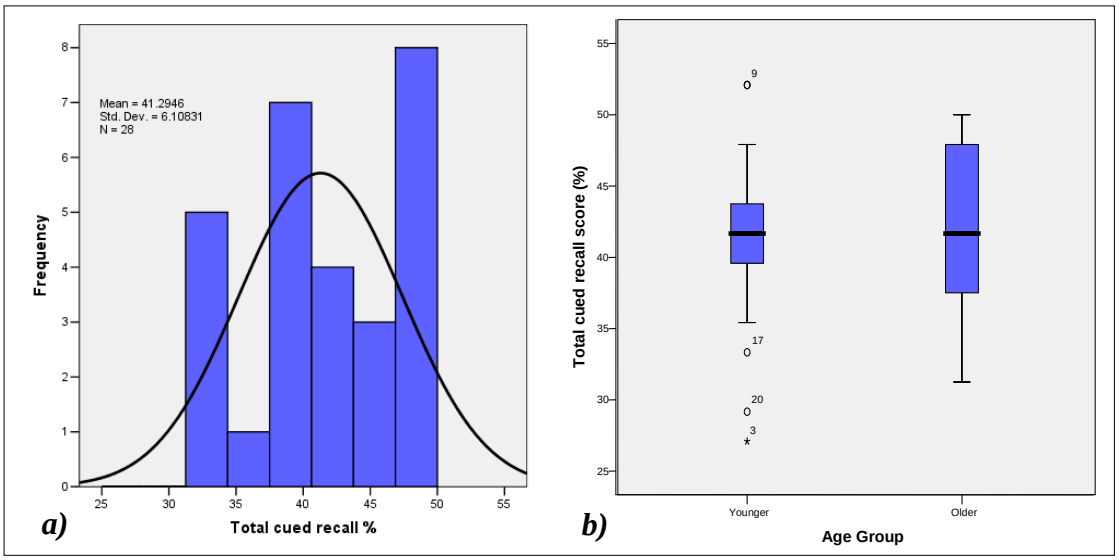


Figure 3.1: Total cued recall performance
a) Older group b) Older relative to Younger

3.2.2 Signal-to-Noise Ratio (SNR)

Data from MEG sensors revealed high SNR, with means of 16.8 (7.36) and 23.5 (8.38) for magnetometers and gradiometers respectively. As with the younger age group, gradiometers had higher SNR than magnetometers (*Magnetometers-Gradiometers: Z=-3.871, p<.001*).

SNR did not differ significantly between age groups, although there was a trend towards lower SNR in magnetometers for older participants (*Younger-Older:*

Magnetometers: Z=-1.72, p=.086; Gradiometers: Z=-0.10, p>.9). The trend in magnetometers was driven by higher signal during the P100m window for younger participants (*Signal SD: Younger-Older: Z=-2.87, p=.004*), rather than a noisier baseline in the older participants (*Baseline SD: Younger-Older: Z=-0.32, p>.7*).

3.2.3 N400m congruency effect

In magnetometers, a significant CE was evident in the SPM of the older group (*Figure 3.2a*), with no suprathreshold differences in the SPM that contrasted the CE across groups. In gradiometer RMS data, in addition to anterior regions detecting significant CE, there was a left posterior region where magnitude of the response appeared larger for words presented in a congruent compared to an incongruent context, contrary to the predicted direction of the effect.

A significant interaction indicated that this effect had greater magnitude in the older compared to younger age group participants (see *Figure 3.2b).* However, comparison of group-average time courses for the original conditions revealed that the effect was in the same direction in both groups (see *Figure 3.2c*). The apparent reversal in direction of the effect in the older group was due to it occurring on top of a large negative deflection (magnetic counterpart of the P1-N2 complex to visual stimuli observed in EEG). In taking the RMS for each original condition in this context, the more negative deflection (e.g. response to 'congruent' stimulus) became of greatest magnitude. The absence of a significant effect in the sensor SPMs for the younger group over this region was due to a less negative P1m-N2m deflection, thus the original waveforms crossed zero during the time window of the effect. When each original condition is a similar distance from zero but in the opposite direction they have similar RMS values and any difference is not seen. For this reason (and because we were interested primarily in differences in evoked responses between conditions, rather than the less experimentally controlled pre-stimulus baseline), we based all subsequent ANOVA comparisons of effect magnitude upon the RMS of the difference between conditions at each location (see 'aim 2' of current chapter and section 1.2.3.2.2 of introduction).

FAL was computed across the 300-600ms time window, chosen to capture the majority of the CE in both groups observed in group average waveforms and inclusive of the time period during which a CE was significant in the sensor SPMs. Significant latency delays were identified for the older relative to younger age group in both sensor types with mean differences of 37ms (SE=10ms) and 33ms (SE=10ms) in magnetometers and

gradiometers respectively (*Magnetometers: Younger-Older: t(47)=-3.73, p=.001; Gradiometers: Younger-Older: t(46)=-3.36, p=.002*). See *Figures 3.3a & 3.4a*.

Given a wide spread of scores in both groups, we selected 200ms-wide time windows, centred at the mean FAL (rounded to closest 50ms) from 350-550ms and 400-600ms in younger and older groups respectively.

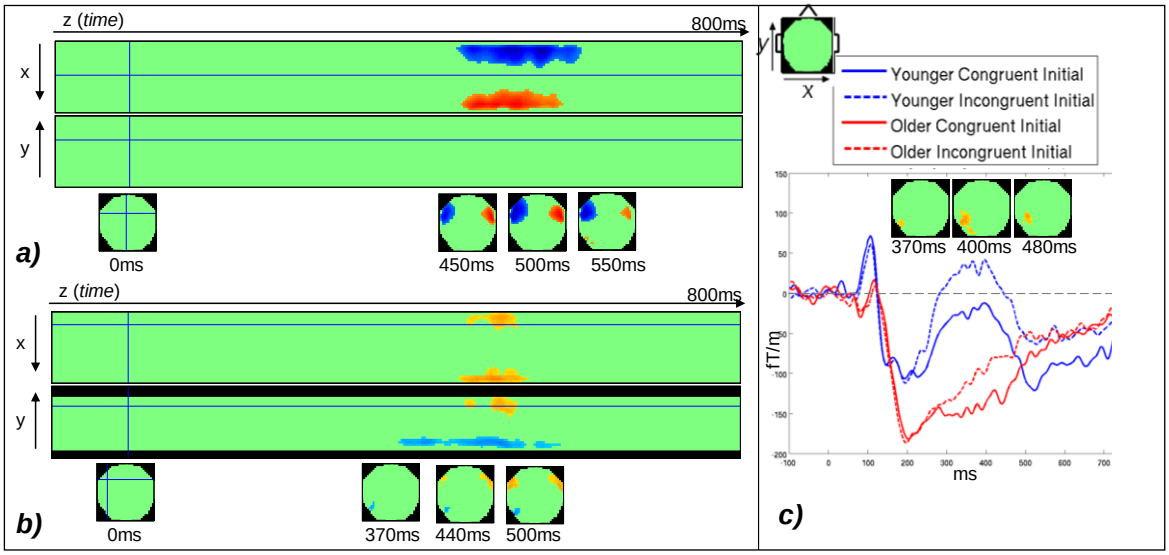


Figure 3.2: Sensor SPMs for Congruency Effect

a) Older group sensor SPM of two-tailed T-test for Congruency Effect in Magnetometers. Threshold: height @ p<.05(FWE corrected); b) Older group sensor SPM for Congruency Effect in Gradiometers RMS. Thresholds: height @p<.001(uncorrected), extent @ p<.05(FWE corrected); c) Unrectified time courses for both groups in temporo-occipital gradiometer MEG172(3), illustrate 'zero-crossing' described above. Dashed line indicates zero magnitude. Snap-shot topographies of older > younger sensor SPM interaction in gradiometers RMS are inset.

3.2.3.1 Magnetometers

There were bilateral regions of increased field power in both fronto- and posterior temporal regions, these did not differ across age groups, so the same ROIs were used (see *Figure 3.3*) and no factor of maxima was incorporated in the analysis. The 3-factor (hemisphere x rostrality x age group) ANOVA revealed a main effect of hemisphere (*F=31.5, p<.001*), with left lateralisation greatest over fronto-temporal sensors, as reflected in an interaction of rostrality with hemisphere (*F=4.78, p=.034*). There were no interactions with, nor main effect of age (having selected appropriate time windows for the effect in each age group). ROI locations are illustrated in relation to the older group average topography in *Figure 3.3d* below, whilst congruency effect magnitude for each group at these ROIs and time courses at the left fronto-temporal ROI (MEG021m) can be found in *Figure 3.3b-c*.

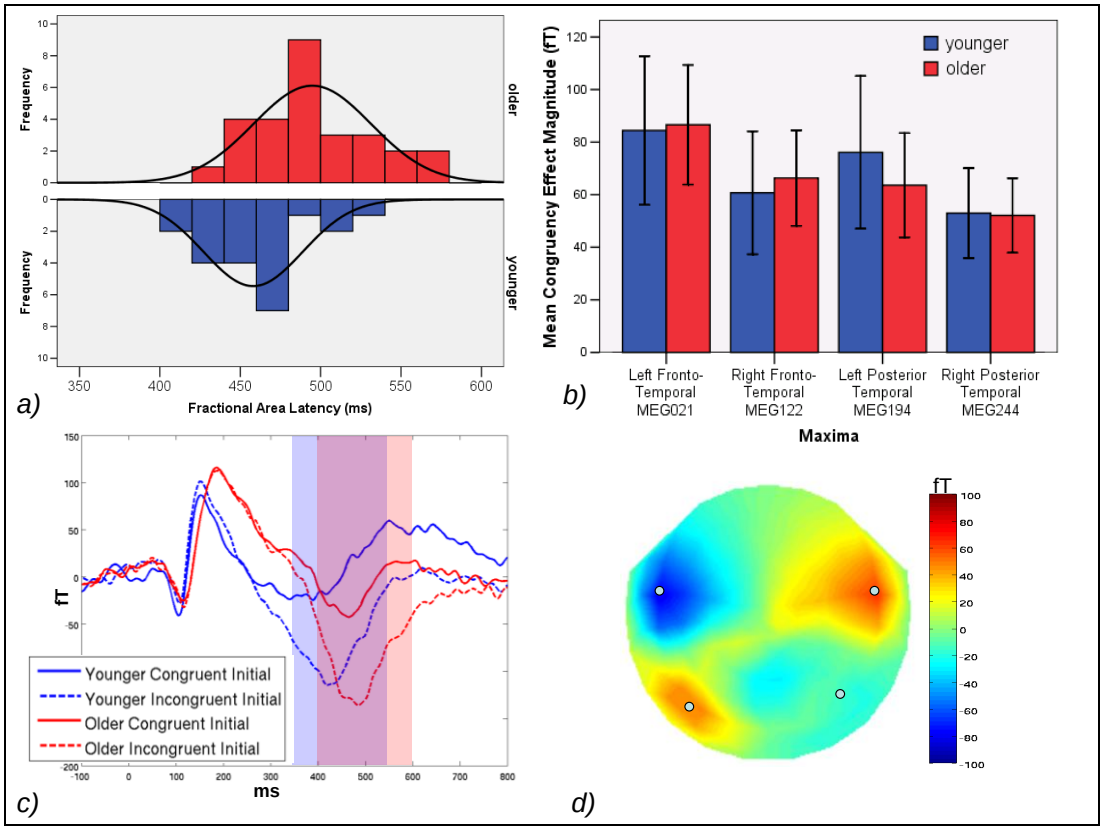


Figure 3.3: Latency and Magnitude of Congruency Effect in Magnetometers
a) Histogram depicting Fractional Area Latency according to age group in left fronto-temporal magnetometer MEG021; b) Mean effect magnitude in maximal sensors for younger & older groups (blue & red bars respectively) across respective time windows. Error bars represent 95% confidence intervals. c) Group average time courses of responses to original conditions in left fronto-temporal maximal magnetometer (MEG021). Shaded areas indicate time window of interest for each group (blue & red for younger & older groups respectively); d) Older group mean CE topography in Magnetometers from 400-600ms. ROIs are highlighted.

3.2.3.2 Gradiometers

Different maxima were seen for younger and older groups: over posterior temporal regions for the younger and over occipital regions for the older (locations depicted in *Figure 3.4e-f*). Anterior maxima coincided across groups, thus the younger group maxima and an adjacent sensor were selected from each hemisphere, in order to make the ANOVA factorial. The omnibus ANOVA revealed main effects of hemisphere ($F=15.3$, $p<.001$), rostrality ($F=5.02$, $p=.030$) and an interaction of hemisphere and rostrality ($=16.2$, $p<.001$), plus a trend for interaction of rostrality with age group ($F=3.86$, $p=.055$). There was an effect of maxima ($F=74.0$, $p<.001$), but this did not interact with age group ($F=0.013$, $p>.9$).

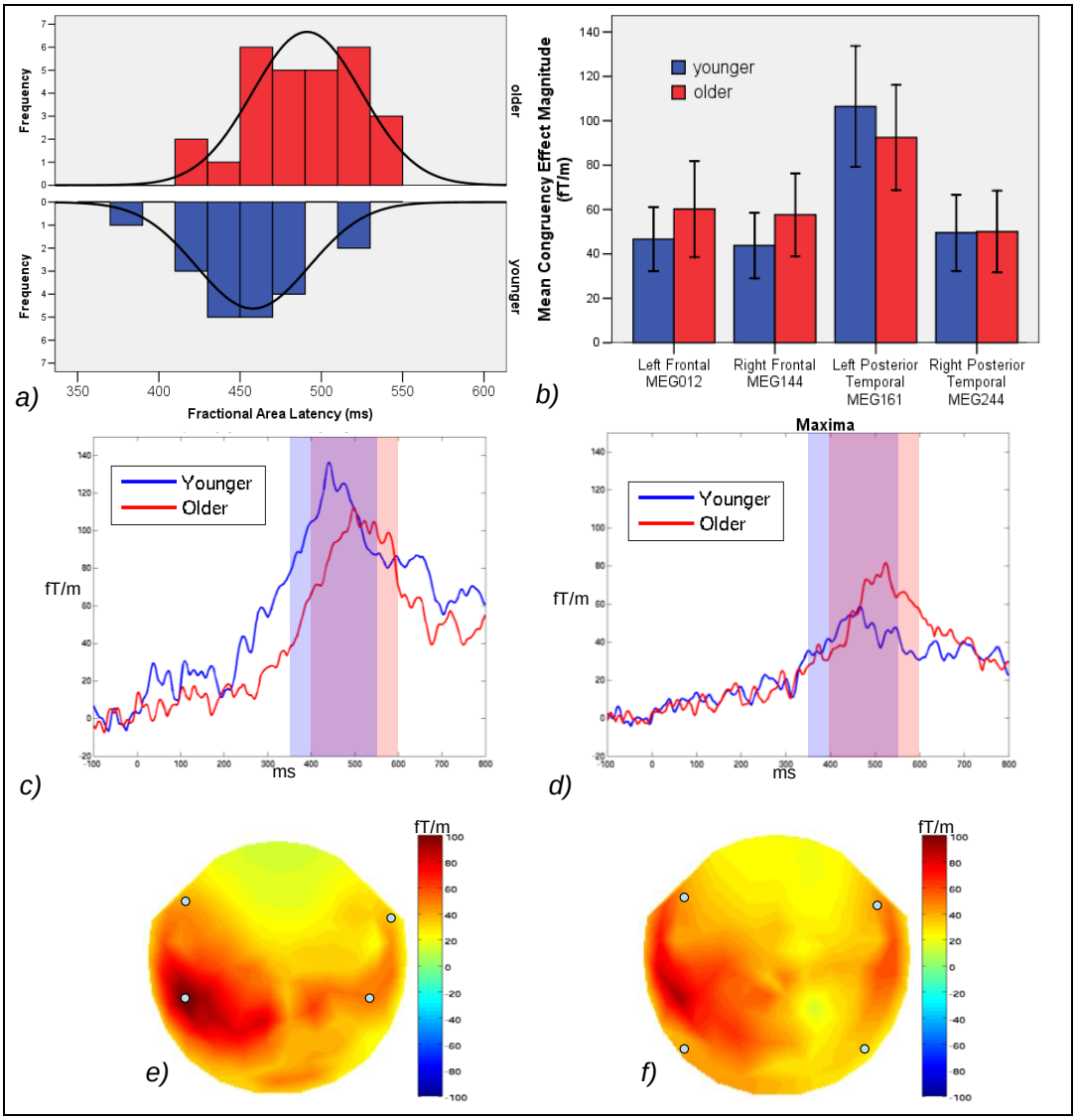


Figure 3.4: Latency and Magnitude of Congruency Effect in Gradiometers

a) Histogram depicting FAL according to age group at left frontal gradiometer MEG012g; b) Mean CE magnitude at selected ROIs (error bars show 95% C.I.); c) & d) Time course of CE (RMS of difference) at left posterior temporal (MEG161g) & frontal (MEG012g) ROIs respectively. Shaded areas indicate time windows of interest, red & blue for Older & Younger groups respectively; e) & f) Younger & Older group mean CE topographies across 350-550ms & 400-600ms respectively (RMS of difference). Group sensor SPM maxima (difference in RMS) are highlighted. Young group maxima were chosen as ROIs.

We identified optimal ROIs, via separate analysis of the 2 levels of rostrality. In anterior sensors there was no effect of age group, therefore younger group maxima were selected as anterior ROIs for patient comparisons. Posterior sensors showed main effects of maxima ($F=65.8$, $p<.001$) and hemisphere ($F=25.5$, $p<.001$), along with a maxima x hemisphere interaction ($F=25.5$, $p<.001$). There was no main effect of, nor interactions with, age group. The group average RMS of difference topographies in *Figures 3.4e-f* demonstrate that the congruency effect at posterior temporal ROIs, the younger group

sensor SPM maxima, were of greater magnitude than at occipital maxima in both groups (when examining the RMS of the effect rather than effect on the RMS), and showed left-sided emphasis. The younger group maxima were therefore selected for use as posterior ROIs in subsequent analyses.

Having identified the younger maxima as optimal to detect the congruency effect in both groups, we used these ROIs to conduct a follow-up hemisphere x rostrality x age group ANOVA, in order to investigate the trend for a rostrality x age interaction identified in the above omnibus ANOVA. As above, main effects of hemisphere and rostrality and a rostrality x hemisphere interaction were identified; additionally, a significant interaction of rostrality with age group was evident (*F=6.80, p=.012*). *Figure 3.4b* depicts effect magnitude increased over anterior sensors and decreased over posterior sensors, for the older relative to younger group on average. However, t-tests revealed no simple effect of age to be significant at either posterior or anterior sensors (all p>.2).

3.2.4 N400m incongruent repetition effect

MEG counterparts of an effect of incongruent repetition were present for the older group in both sensor types, as depicted by sensor SPMs in *Figure 3.5a* below. When comparing with the younger group, there was a brief suprathreshold difference in gradiometer RMS, with the older group showing increased right anterior IRE magnitude relative to the younger group from 475-510ms (*Figure 3.5c*).

This difference in IRE magnitude may have reflected significant latency delay in the older relative to younger group, with mean differences of 54ms (S.E. 10ms) and 28ms (S.E. 10ms) for magnetometers and gradiometers respectively. (*FAL 300-600ms: Magnetometers: t(44)=-5.34, p<.001 (2 outliers in the younger group were removed); Gradiometers: t(45.501)=-2.71, p=.010*). As shown in *Figure 3.7a*, however, there was a suggestion of a bimodal distribution of FAL in gradiometers for the older group, thus the mean value may not necessarily give an accurate description of time differences between younger and older individuals. Nonetheless, since the estimate of latency difference in this effect (and congruency effect) was close to the 50ms difference estimated in the EEG literature (Olichney, et al., 2006; Olichney, Morris, et al., 2002; Olichney, Taylor, Gatherwright, et al., 2008), we stuck with a 50ms shift of time windows for simplicity. Thus, we used time windows identical to those defined for the congruency effect, i.e. 350-550ms and 400-600ms for younger and older group ROIs respectively.

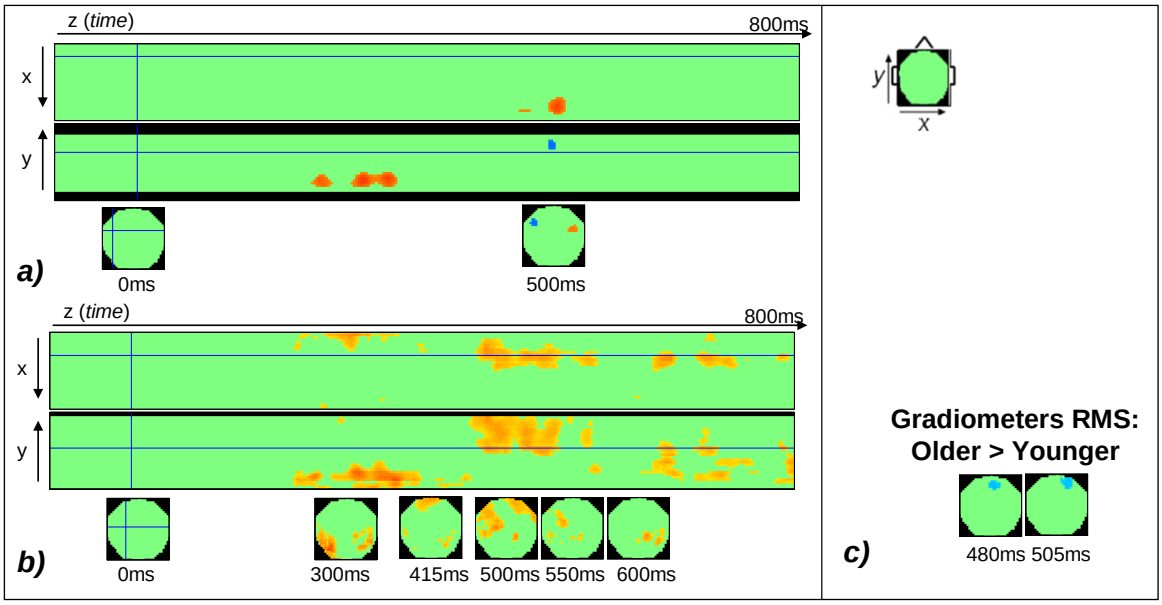


Figure 3.5: Sensor SPMs for Incongruent Repetition Effect
a) Older group sensor SPM for two-tailed T-test of IRE in Magnetometers. Threshold: height @ p<.05(FWE corrected); b) Older group sensor SPM for two-tailed T-test of IRE in Gradiometers RMS. Thresholds: height @p<.001(uncorrected), extent @ p<.05(FWE corrected); c) Snap-shot topographies of older > younger sensor SPM interaction in gradiometers RMS.

3.2.4.1 Magnetometers

Bilateral posterior and anterior ROIs were identified from the SPMs. As the older group maxima coincided with those of the younger group, there was no further factor of maxima in this analysis. ANOVA indicated main effects of both hemisphere (*F=5.78, p=.020*) and rostrality (*F=4.89, p=.032*), such that emphasis was left-sided and posterior, see *Figure 3.6d*. As observed for the younger group, the topography was very similar to that of the CE. Despite a suggestion of a reduced IRE over the left posterior temporal ROI in the older group (*Figure 3.6b*), any interactions or main effect of age did not reach significance. A follow-up t-test revealed a trend in this direction which did not reach significance (*t(47)=1.921, p=.061*).

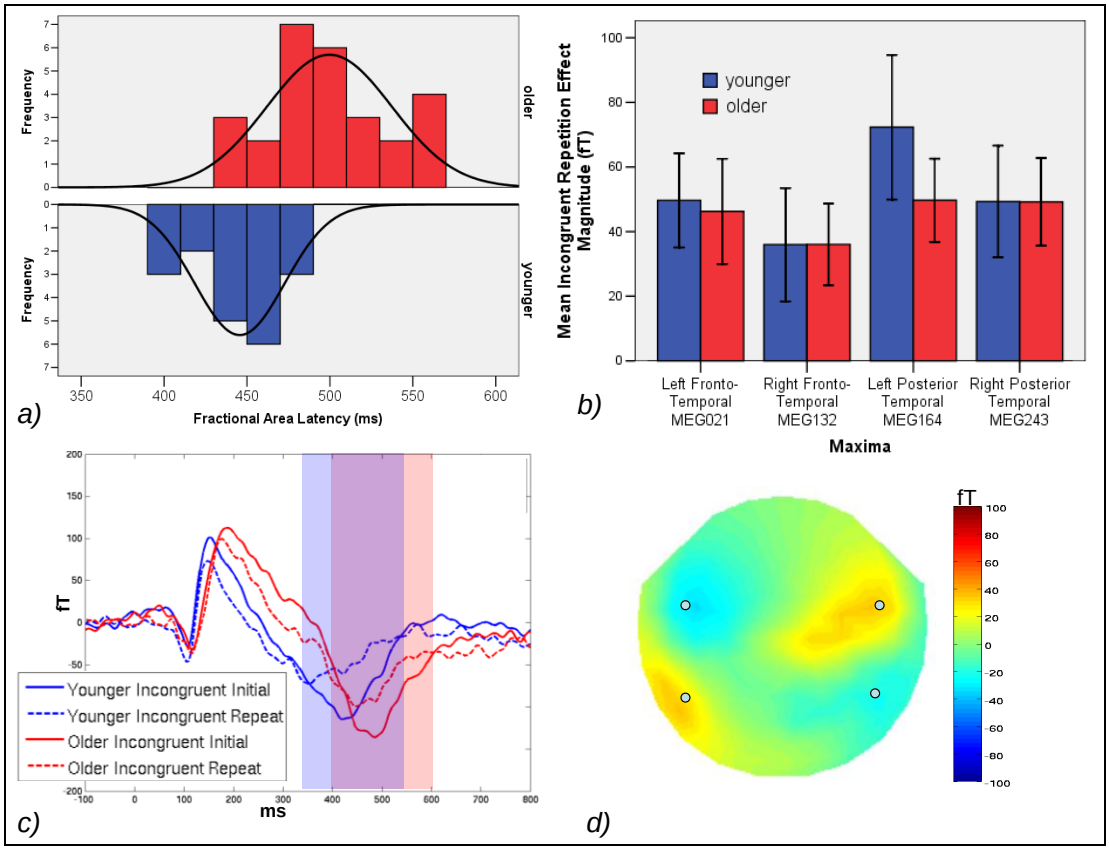


Figure 3.6: Incongruent Repetition (N400m) Effect in magnetometers
a) Histogram depicting FAL according to age group at left fronto-temporal ROI MEG021m; b) Mean IRE magnitude in ROIs for younger & older groups (blue & red bars respectively). Error bars represent 95% confidence intervals. c) Group average time courses of responses to original conditions in left fronto-temporal maximal ROI (MEG021m). Shaded areas indicate time window of interest for each group (blue & red for younger & older groups respectively); d) Older group mean topography for IRE in magnetometers from 400-600ms. ROIs are highlighted.

3.2.4.2 Gradiometers

Bilateral frontal and posterior temporal ROIs coincided across groups (locations indicated in *Figure 3.7d*) and analyses were conducted without the factor of maxima. ANOVA revealed a main effect of rostrality ($F=64.4$, $p<.001$) but only trends towards an effect of hemisphere ($F=3.47$, $p=.069$) and an interaction of hemisphere and rostrality ($F=2.86$, $p=.097$). Follow-up t-tests confirmed left lateralisation over posterior-temporal sensors only (*L-R: Frontal:* $t(47)=1.45$, $p>.1$; *Posterior Temporal:* $t(47)=2.01$, $p=.050$). An interaction of rostrality and age group ($F=5.65$, $p=.022$) indicated that the younger group tended to demonstrate relatively greater posterior temporal relative to frontal IRE magnitude than the older group (see *Figure 3.7b*); similar to the pattern found for the CE. However, as for the CE, a simple effect of age group was not significant at any of these ROIs (*all* $p>.5$). Group average time courses for the IRE at the left posterior temporal ROI (MEG161g) are shown in *Figure 3.7c*.

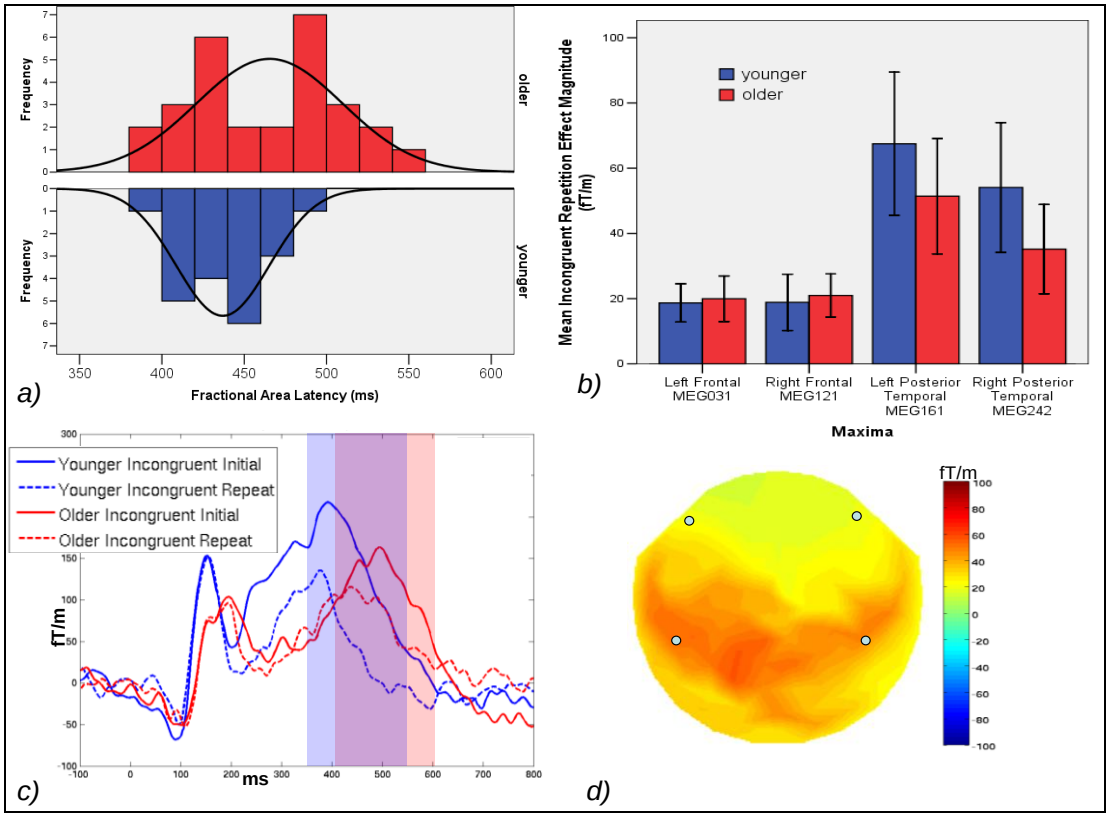


Figure 3.7: Incongruent Repetition Effect in Gradiometer Maxima

a) Histogram depicting FAL according to age group in left posterior temporal maximal ROI MEG161g; b) Mean IRE magnitude in ROIs for younger & older groups (blue & red bars respectively). Error bars represent 95% confidence intervals. c) Group average time courses of responses to original conditions in unrectified left posterior temporal gradiometer (MEG161(2)). Shaded areas indicate time window of interest for each group (blue & red for younger & older groups respectively); d) Older group mean topography for IRE in gradiometers from 400-600ms. ROIs are highlighted.

3.2.5 P600m Congruent Repetition Effect

For both types of MEG sensor, a CRE during the 550-800ms window was present in the older group (*Figure 3.8a-b*). A small region of increased effect magnitude for older relative to younger individuals was evident over left posterior temporal regions between 500 and 600ms in gradiometers RMS (*Figure 3.8c*). Unlike the CE and IRE, the latency of the CRE did not significantly differ between groups in either type of MEG sensor, with mean differences of *17ms (S.E.=11ms) and 13ms (S.E.=10ms)* in magnetometers and gradiometers respectively (*Younger-Older: Magnetometers: t(47)=-1.59, p>.1; Gradiometers: t(46)=-1.39, p>.1*), see *Figures 3.9a,c* and *3.10a,c*. We therefore kept the 550-800ms time window used in prior studies (Olichney, Morris, et al., 2002; Van Petten, et al., 1991) to examine this effect across both groups.

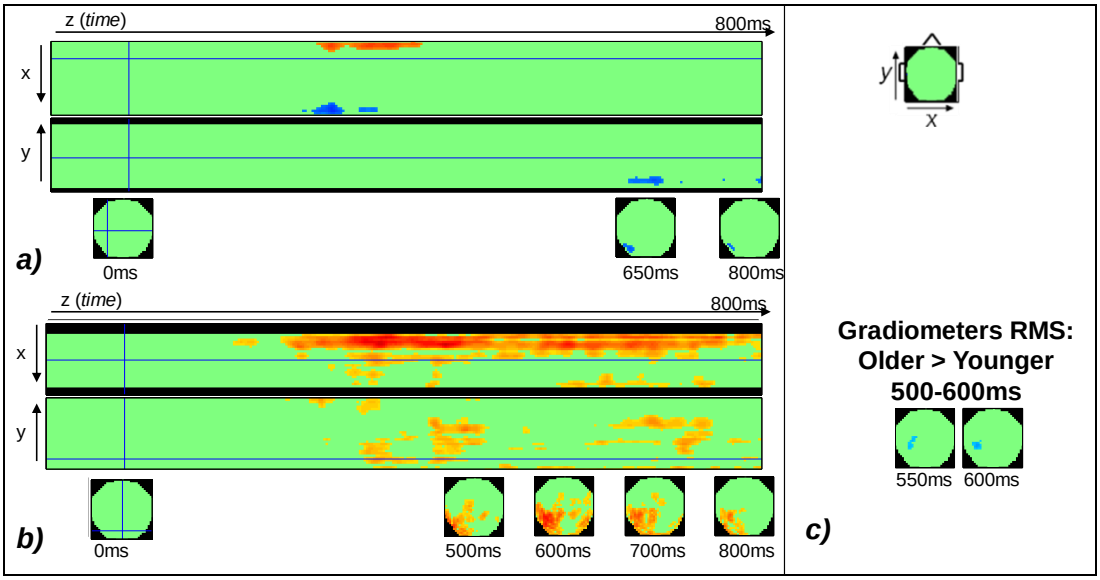


Figure 3.8: Sensor SPMs for Congruent Repetition Effect

a) Older group sensor SPM for two-tailed T-test of CRE in magnetometers. Threshold: height @ p<.05(FWE corrected); b) Older group sensor SPM for two-tailed T-test of CRE in gradiometers RMS. Threshold: height @p<.001(uncorrected), extent @ p<.05(FWE corrected); c) Snap-shot topographies of older > younger sensor SPM interaction in gradiometers RMS.

3.2.5.1 Magnetometers

Although the conservative FWE height-corrected sensor SPMs revealed only a left posterior maximum in the older group and a left fronto-temporal maximum in the younger group, anterior and posterior maxima were selected bilaterally with reference to less stringently-corrected sensor SPMs (p<.001 for height, uncorrected, and p<.05 for extent, FWE-corrected). The locations of these maxima did not differ between groups therefore no factor of maxima was incorporated in the ANOVA. No significant main effects or interactions were identified. See *Figure 3.9b-d* for ROI locations and magnitudes and time course in left parieto-occipital ROI MEG173m.

3.2.5.2 Gradiometers

Significant effects were evident only over left posterior temporal sensor regions; thus there was no rostrality factor in this comparison. The area of significant effect in sensor SPMs was more widespread for the older than younger group, therefore older group maxima were defined slightly anterior to the younger group maxima (which actually coincided across groups). Homologues from the right hemisphere were selected for each of these maxima, in order to enable the factor of hemisphere to be examined between groups.

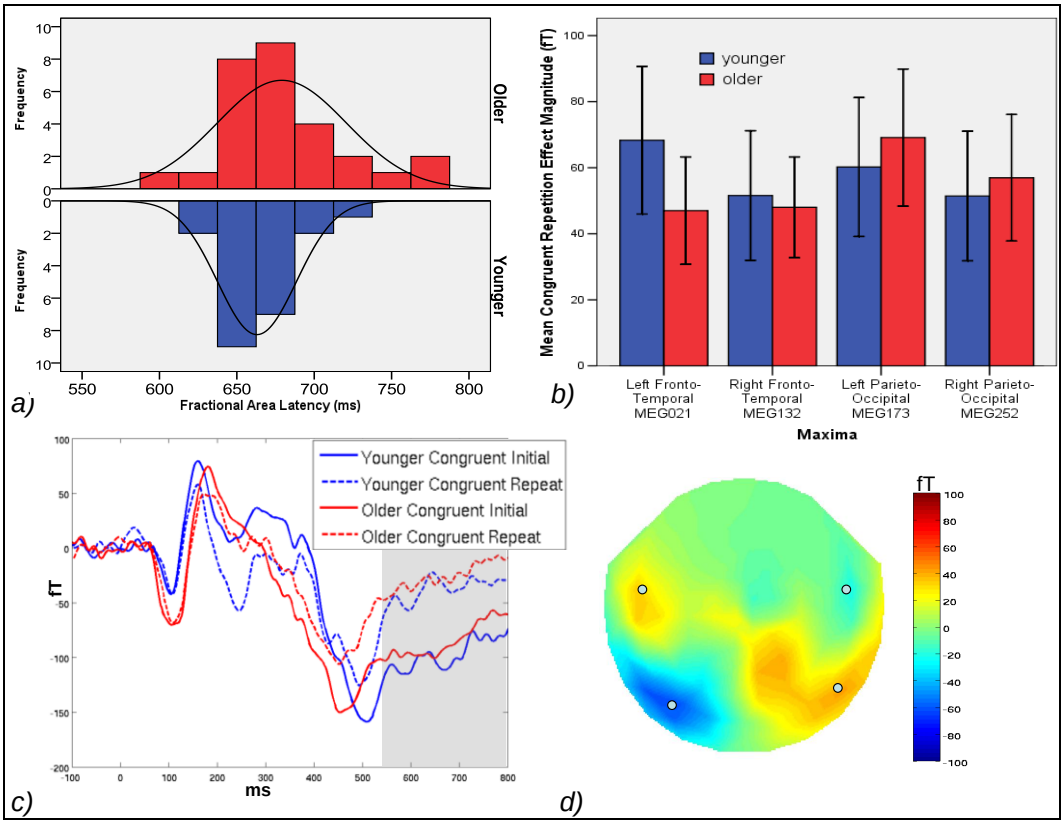


Figure 3.9: Congruent Repetition (P600m) Effect in Magnetometers

a) FAL according to age group at left parieto-occipital ROI MEG173m; b) Mean effect magnitude in ROIs for younger & older groups (blue & red bars respectively). Error bars represent 95% confidence intervals. c) Group average time courses of responses to original conditions in left parieto-occipital maximal ROI (MEG173m). Shaded area indicates time window of interest. d) Older group mean topography for CRE in Magnetometers from 550-800ms. ROIs are highlighted.

ANOVA indicated main effects of hemisphere (*F=13.3, p=.001*) and age group (*F=5.28, p=.026*), indicating larger CRE magnitude on the left and in the older group. However, it appeared that this might have been due to heightened effect magnitude in the older group at the 'older', but not 'younger' maxima (*Figure 3.10b*), implicating more widespread effect topography in the older group. Indeed, when 'older group' maxima were removed from the comparison, the effect of age group was no longer significant (*F=1.51, p>.2*), see time courses at left posterior temporal ROI MEG164g in *Figure 3.10c*, but the hemispheric difference remained (*F=15.5, p<.001*). As the CRE did not significantly differ between groups at the younger group maxima, these were chosen as ROIs (locations depicted in *Figure 3.10d).*

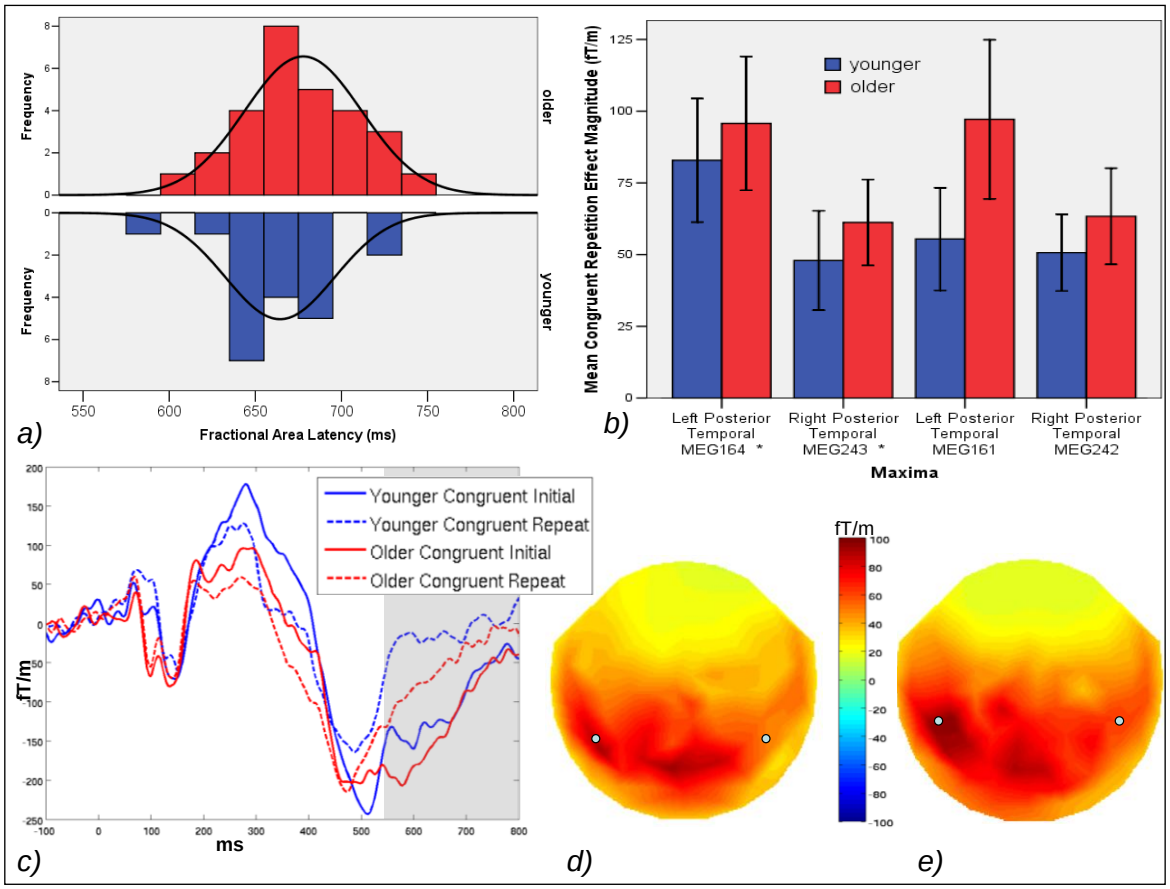


Figure 3.10: Congruent Repetition (P600m) Effect in Gradiometers

a) Histogram depicting FAL according to age group in left posterior temporal ROI MEG164g; b) Mean effect magnitude in maximal sensors for younger & older groups (blue & red bars respectively) across time window. Error bars represent 95% confidence intervals. Bars marked with an asterisk (, 'younger group' maxima) were retained as ROIs; c) Group average time courses of responses to original conditions in unrectified left posterior temporal gradiometer MEG164(3). Shaded area indicates time window of interest; d) & e) Younger & Older group mean CRE RMS topographies, 550-800ms. Group maxima are highlighted, younger group maxima were retained as ROIs.*

3.2.6 Early Repetition Effect

Sensors SPMs for the older group data depicted a main effect of repetition from around 200-350ms in magnetometers and persisting throughout the epoch from170ms in gradiometers RMS (*Figure 3.11a-b*). This was indifferent to item congruency until around 540ms in magnetometers and 400ms in gradiometers RMS (except for a brief right frontal congruent word advantage from 300-310ms, likely to be spurious). In gradiometer RMS, from 245-265ms in right anterior sensors, the older group demonstrated increased RE magnitude compared with the younger group (*Figure 3.11c).*

There were no significant age-group related differences in latency, with mean differences of 2ms (SE=10ms) and 7ms (SE=11ms) in magnetometers and gradiometers respectively (*Younger-Older: MEG151m: t(47)=-0.148, p>.8; MEG161g: t(46)=0.574,*

p>.5), see *Figures 3.12a* & 3.*13a*. This held true in magnetometers (where significant group topographic differences existed, see section 3.2.6.1 and *Figure 3.12b*) when FAL was measured from each group's own maximum, with a mean difference of 16ms (SE=10ms), (*Younger(MEG164m)-Older(MEG151m): t(47)=-1.61, p>.1*). The 200-400ms time window was chosen to examine this effect in both groups based upon consultation of time courses at ROIs depicted in *Figures 3.12c* & *3.13c*.

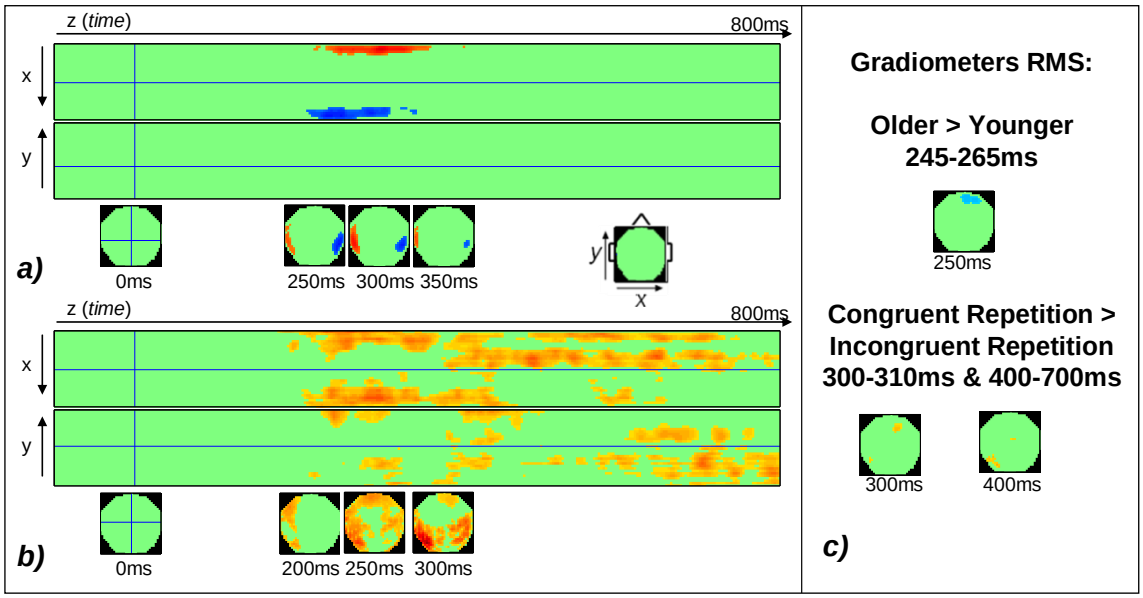


Figure 3.11: Sensor SPMs for Main Repetition Effect

a) Older group sensor SPM of two-tailed T-test for Main Repetition Effect in magnetometers. Threshold: height @ p<.05(FWE corrected); b) Older group sensor SPM of two-tailed T-test for Main Repetition Effect in gradiometers RMS. Threshold: height @p<.001(uncorrected), extent @ p<.05(FWE corrected); c) Snap-shot topographies from gradiometers RMS of older > younger interaction & congruent-incongruent repetition effect interaction in older group.

3.2.6.1 Magnetometers

A single maximum channel was identified in each hemisphere for each group; these were located above mid-temporal and posterior temporal regions for older and younger groups respectively. No rostrality factor was incorporated in the ANOVA which revealed an interaction of maxima with age group (*F=21.5, p<.001*). As indicated in *Figure 3.12b*, the older group demonstrated greater RE magnitude than the younger group at mid-temporal maxima, whereas the converse was true at the posterior temporal locations. Given this topographical difference according to age, older group maxima were selected as ROIs for subsequent patient comparisons, although we note that this did compromise the independence of these ROIs from the older group data set. See *Figure 3.12c-d* for time courses at left mid-temporal ROI MEG151m and ROI locations in relation to group average RE topographies.

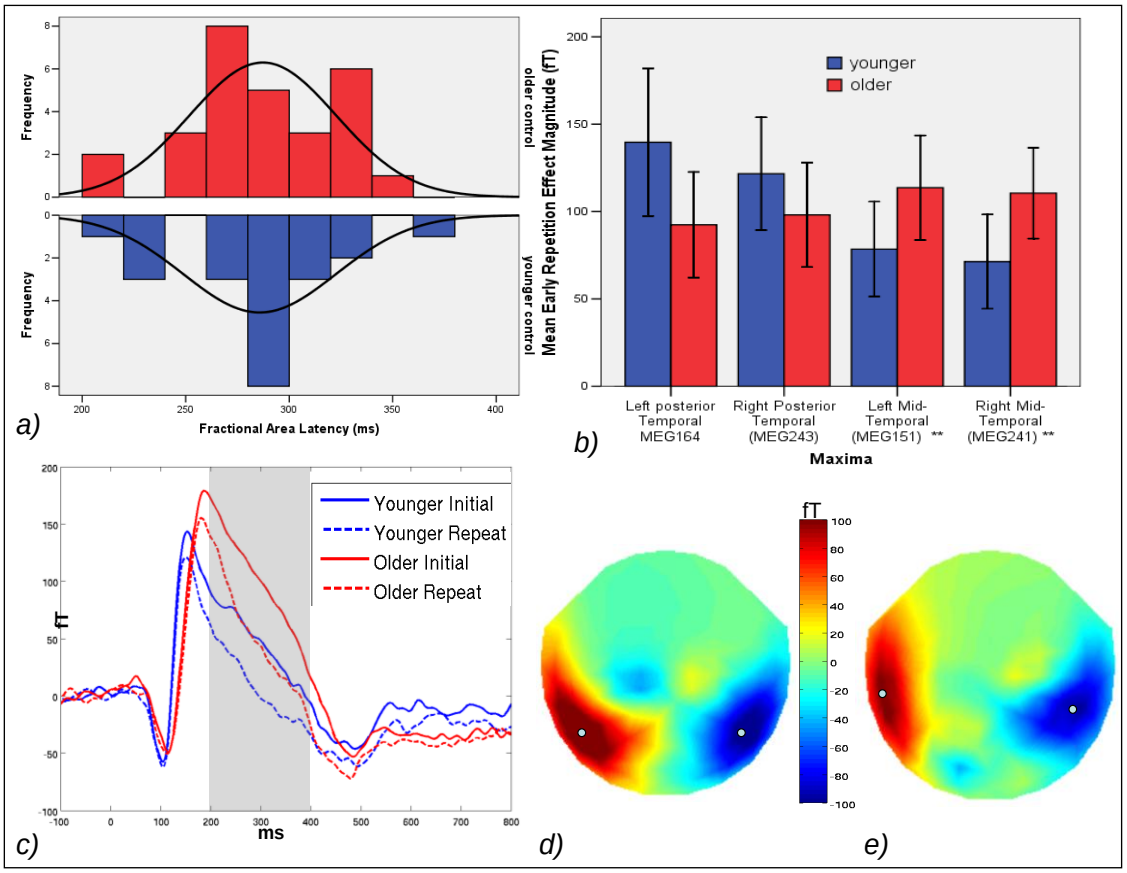


Figure 3.12: Early repetition Effect in Magnetometers

a) Histogram depicting FAL according to age group in left mid-temporal magnetometer MEG151m; b) Mean RE magnitude in maximal sensors for younger & older groups (blue & red bars respectively) across 200-400ms time window. Error bars represent 95% confidence intervals. Older group maxima marked with asterisk (**) were retained as ROIs. c) Group average time courses of responses to original conditions in left mid-temporal ROI (MEG151). Shaded area indicates time window of interest. d) & e) Younger & Older group mean RE topographies in Magnetometers, 200-400ms respectively. Group maxima are highlighted, older group maxima were retained as ROIs.

3.2.6.2 Gradiometers

No factor of maxima was incorporated into this analysis. Parieto-occipital ROIs were identified bilaterally from sensor SPMs for both groups, along with left fronto-temporal and right frontal ROIs (*Figure 3.13c-d;* time courses are from left parieto-occipital gradiometer MEG173(3), and the ROI locations are indicated on the older group average topography). The right anterior ROI was significant in the sensor SPM for the older group only. ANOVA revealed a main effect of rostrality ($F=88.2$, $p<.001$), such that posterior ROIs showed greater RE magnitude than anterior ROIs, as illustrated in *Figure 3.13b*. A trend suggesting greater RE magnitude on the left did not attain significance ($F=3.423$, $p>.07$), nor were there any main effects or interactions with age group.

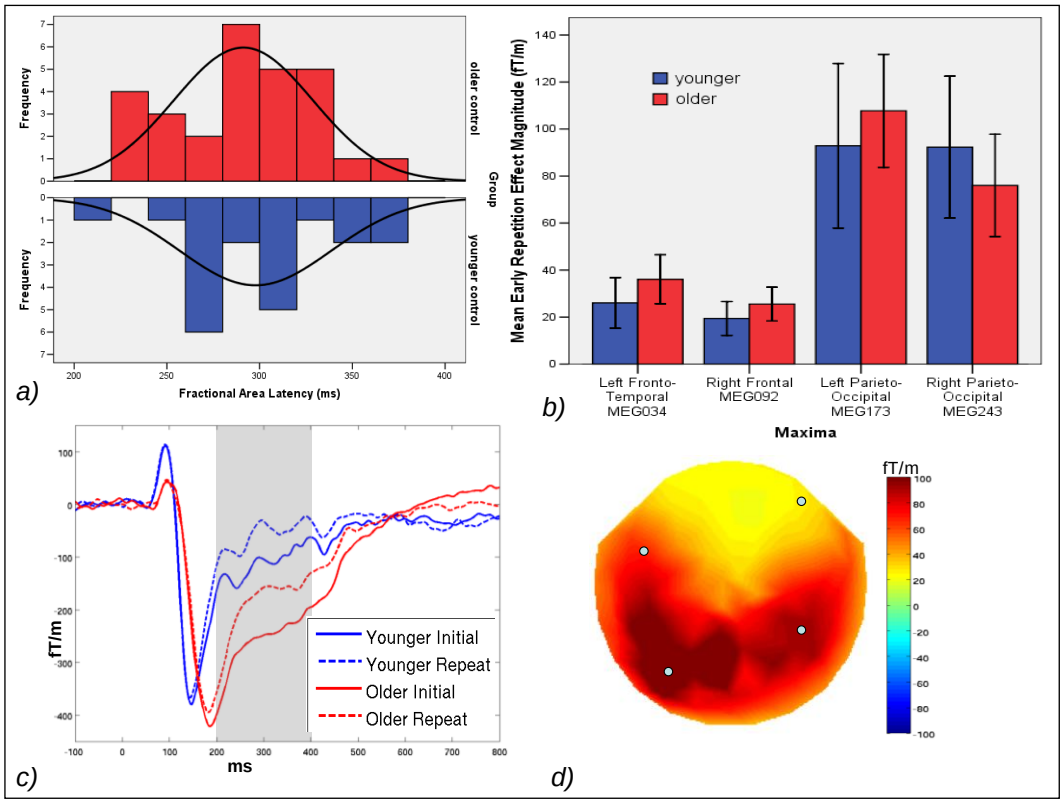


Figure 3.13: Early Repetition Effect in Gradiometers

a) Histogram depicting FAL across time window 150-400ms according to age group at left parieto-occipital ROI MEG173g; b) Mean RE magnitude in ROIs for younger & older groups (blue & red bars respectively). Error bars represent 95% confidence intervals. c) Group average time courses of responses to original conditions in unrectified left parieto-occipital gradiometer MEG173(3). Shaded area indicates time window of interest. d) Older group mean RE gradiometers RMS topography, 200-400ms. ROIs are highlighted.

3.3 Chapter Summary

Equivalent performance for the MEG congruency task and, contrary to expectations, the cued recall task, was observed across age groups. Our aims were to characterise the impact of age upon, and topographical distribution of, our effects of interest, and to define spatio-temporal ROIs that could be used to examine data from patient groups. Findings are summarised below and the ROIs we defined are listed in *Table 3.1*.

3.3.1 N400m congruency effect

Older participants had a delayed N400m congruency effect relative to younger participants (Aim 1), and with time windows adjusted to accommodate this, there were no overall differences in magnitude according to age group (Aim 1). Some topographic differences were evident in gradiometers: the older group tended towards increased effect over frontal and reduced CE over posterior temporal ROIs relative to their younger

counterparts. The CE was greater in left than right hemisphere ROIs for both groups (Aim 2), in gradiometers this left lateralisation was confined to posterior regions.

Apparent topographic differences in sensor SPM maxima according to age-group (see *Figure 3*.2b) for the effect in gradiometers RMS were in fact due to differences in original non-contrasted conditions, as discussed above. When taking the RMS of the effect, the younger group maxima showed greatest CE magnitude and were comparable in both groups. Therefore, ROIs that should be most sensitive to the CE in the patients (Aim 3) were defined from the young group.

Table 3.1: Spatio-temporal ROIs

	Time window	Sensor locations			
		Magnetometers		Gradiometers	
Congruency Effect	400-600ms *	Fronto-Temporal MEG021m MEG122m	Posterior Temporal MEG194m MEG244m	Frontal MEG012g MEG144g	Posterior Temporal MEG161g MEG244g
Incongruent Repetition Effect	400-600ms *	Fronto-Temporal MEG021m MEG132m	Posterior Temporal MEG164m MEG243m	Frontal MEG011g MEG132g	Posterior Temporal MEG161g MEG242g
Congruent Repetition Effect	550-800ms	Fronto-Temporal MEG021m MEG122m	Parieto-Occipital MEG173m MEG252m		Posterior Temporal MEG164g MEG242g
Early Repetition Effect	200-400ms		Mid-Temporal * MEG151m MEG241m	Fronto-Temporal MEG021g MEG132g	Parieto-Occipital MEG173g MEG242g

Gradiometer ROIs were defined based on RMS of difference.
** denotes location or time window defined from older group data*

3.3.2 N400m incongruent repetition effect

The older group on average demonstrated longer IRE latencies than the younger group (Aim 1). At the magnetometer ROI this was comparable to the latency difference for the CE, whilst a smaller latency difference and bimodal distribution was evident at the gradiometer ROI. For simplicity, the same time windows were selected as for the CE, i.e. 350-550ms & 400-600ms for younger and older respectively. As seen for the CE, an interaction between age group and rostrality was suggestive of a posterior-anterior shift with ageing (Davis, et al., 2008), but was unsupported by simple age effects at any

individual location (Aim 1). The IRE was emphasised in left more than right magnetometer ROIs and at posterior temporal gradiometer ROIs, without any reliable differences according to age group (Aim 2). Younger and older group maxima coincided for this effect therefore these were used as ROIs (Aim 3).

3.3.3 P600m congruent repetition effect

CRE did not significantly differ in terms of latency or magnitude according to age group (Aim 1), but differed topographically, in that the older group demonstrated a more diffuse CRE in posterior gradiometers than the younger group. There was a left-sided emphasis in gradiometers (Aim 2), equivalent across both groups, and ROIs (Aim 3) were defined from the younger group maxima.

3.3.4 Early repetition effect

There were no significant group-related differences in magnitude or latency of this early repetition effect (Aim 1), however topographical differences were evident in magnetometers, but not in gradiometers. In order to conduct subsequent comparisons with (older-aged) patient groups (Aim 3), magnetometer ROIs were selected from the older group maxima and gradiometer ROIs from the younger group maxima. The emphasis in gradiometers was greatest at parieto-occipital sensors where lateralisation was not evident (Aim 2).

Chapter 4
Active memory paradigm in probable Alzheimer's disease patients

The following chapter examined MEG effects of interest, for which spatio-temporal ROIs were identified in the previous chapter, in a group of individuals diagnosed with mild probable Alzheimer's disease (pAD). These data were compared with those of the older controls (control group) studied in the last chapter. The ultimate aim was to define metrics with maximal sensitivity and specificity to pAD, that could be subsequently used (in chapter 5) to identify individuals experiencing mnemonic symptoms as a result of incipient dementia.

Aims & predictions

Aim 1. Identify latency or magnitude differences between patients and controls

For each effect of interest, latency and magnitude were compared between pAD and control groups, at the spatio-temporal ROIs defined in the previous chapter. We predicted increased latency and diminished magnitude for the N400 semantic congruity effect (CE) in patients diagnosed with pAD relative to controls, as has been reported previously (Iragui, Kutas, & Salmon, 1996; Schwartz, Kutas, Butters, Paulsen, & Salmon, 1996).

We expected to replicate in MEG the finding that magnitude of EEG N400 and P600 effects to repetition were diminished or absent in patients with Alzheimer's-type dementia (Olichney, et al., 2006; Olichney, Taylor, Gatherwright, et al., 2008). Whilst this diminution of the P600 repetition effect (CRE) is believed to reflect impairment of explicit, episodic memory processes, attenuation of the N400 repetition effect (IRE) has been suggested to reflect injury to more implicit memory processes, such as an inability to benefit from contextual cues that hasten semantic search. Given the novelty of the early repetition effect, there were no strong predictions as to whether it would differ between groups.

Aim 2. Identify MEG methods for classifying pAD and control individuals

We aimed to devise a metric, based upon those MEG measures identified as differing between pAD and control groups, predictive of diagnostic category. Olichney et al., (2006) were able to discriminate individuals with pAD from controls, using EEG measures of the N400 and P600 repetition effects (IRE and CRE). Their metric categorised participants as normal if both N400 and P600 repetition effect amplitudes

were at or above the 10th percentile of the healthy population (measured at electrodes T6 and Pz respectively), achieving 100% sensitivity and 82% specificity to pAD. A longitudinal study by the same laboratory found that in patients with a diagnosis of mild cognitive impairment, this metric demonstrated 81% (13/16) sensitivity and 80% (8/10) specificity to conversion to pAD within 3 years (Olichney, Taylor, Gatherwright, et al., 2008).

Our first approach replicated the method used in the studies described above, involving computation of 10th percentile cut-offs for all measures that differed significantly between pAD and control groups and assessment of how well these thresholds discriminated between groups. While there was an element of circularity in the approach adopted here – first defining effects that differ reliably between patients and controls, and then calculating their sensitivity and specificity (not to mention a multiple comparison problem) – the utility of these metrics was intended to be tested in the second, larger group considered in chapter 5 (i.e. to distinguish individuals whose memory complaints are due to incipient dementia from those whose subjective memory loss is attributable to other causes, such as anxiety and/or depression). In other words, the pAD patients in the present chapter constituted a "training" dataset from which to derive a classification method.

To derive another metric that could be used to predict the probability of an individual having dementia of the Alzheimer's type, we applied a backwards step-wise logistic regression procedure. This method incorporated the identified MEG measures as predictors of group membership and excluded any predictors that did not significantly improve the accuracy of the 'model' that classified pAD patients and controls, thus enabling us to derive the most parsimonious and accurate solution from the available data. The output is a probability function, which described in this case the likelihood of an individual having pAD (as defined by the characteristics by which the pAD patients and controls in our sample differed reliably).

4.1 Method

4.1.1 Participants

Eight individuals (6 males) with a diagnosis of pAD volunteered to participate after receiving an invitation from a neurologist, following attendance at an early dementia clinic at a regional hospital. All were right-handed and ranged in age from 60 to 80 years with a mean age of 71.2 years (SD=7.8 years). Age did not significantly differ between

these patients (the 'pAD' group) and the controls ('control' group), who were the older group in the previous chapter (*pAD-control: t(34)=0.905, p>.37*). Patients' participation in this study was approved by a local NHS regional ethics committee (LREC code: 08/H0306/068). All gave written informed consent. They were unpaid for their participation but received reimbursement of travel expenses and light refreshments during their visits. As part of standard clinical procedure, patients had undertaken the ACE-R during visits to a memory clinic prior to participating in the current study.

4.1.2 Procedure

The MEG active memory task and procedure were identical for patient and control groups, with the exception that in this case only 3 EEG electrodes, referenced to the nose (Cz, P3 and P4 from the standard 10-20 montage), were applied. As was the case for the control group, EEG data were consulted only informally to check qualitatively for N400 and P600 components, and are not reported further here. During subsequent behavioural testing, the pAD group performed both free-recall and cued recall, whereas the control group had performed only cued recall, without any preceding free recall task.

4.1.3 Analysis approach

Pre-processing of MEG data and calculation of SNR were identical to those used for control group data. Non-parametric tests (Mann-Whitney U-test and Wilcoxon signed ranks) were used for SNR comparisons between groups and sensor types. As noted previously, our SNR measure used magnitude of the P100m as our 'signal' measure; SNR comparisons between groups may therefore be confounded by differences in P100m magnitude.

4.1.3.1 Latency and selection of time windows of interest

Fractional area latency (FAL) was computed as described in previous chapters at the ROI which detected maximal effect magnitude in the control group for each sensor type. The time windows used were those defined for the control group: 400-600ms for N400m effects, 550-800ms for the P600m congruent repetition effect and 200-400ms for the early repetition effect. FAL measures were used to conduct t-tests in order to detect group differences.

4.1.3.2 Single-channel analyses

Our approach to group comparisons differed in this chapter from the preceding chapters, as we no longer factorised spatial location. Having defined ROIs in a principled manner, we now simply compared magnitude between patient and control groups separately at each ROI for each effect of interest, via t-tests. The advantage of this approach was that we no longer needed to take the absolute magnitude in magnetometers, conferring sensitivity to the direction of the difference at each ROI and enabling detection of cases where polarity of the effect was reversed. This sensitivity to direction of the effect was not possible using RMS of the difference in gradiometers, which was however necessary for the reasons detailed in the preceding chapter.

For all effects of interest, except for the early repetition effect for which there was no pre-existing literature, we expected to uncover reduced effect magnitude in the pAD relative to control group. One-tailed tests were therefore utilised for all comparisons apart from those concerning the early repetition effect.

4.1.3.3 10^{th} percentile cut-offs

The 10^{th} percentile for effect magnitude within the control group was computed for each measure identified as differing significantly between pAD and control groups in the previous analysis step. Any individual data point that fell below the cut-off for each effect was classified as 'low'. Sensitivity to the diagnosis of pAD (proportion of patient cases correctly classified) was computed for each measure (specificity was constant, as we selected the 10^{th} percentile based on control data), and the most sensitive measure for each effect of interest was selected. The count of 'low' measures from these 4 variables was computed for each participant and these were examined according to group to uncover the threshold, in terms of number of 'low' measures, for optimal sensitivity and specificity to pAD.

4.1.3.4 Logistic regression

MEG effects identified in preceding steps as differing significantly between pAD and control groups were converted to standardised z-scores, based upon the mean and standard deviation of those effects within the control group. Variables were standardised in this manner prior to logistic regression analysis, in order to ensure comparable parameter estimates across all predictor variables.

Group (pAD or control) was used as the dependent categorical variable for an independent logistic regression analysis. Logistic regression was performed in two stages, in order to minimise the number of independent variables entered into the model simultaneously, thus avoiding over-fitting of the model to the data. Our primary goal was to arrive at the model that provided the most parsimonious and accurate discriminatory function between controls and patients.

Firstly, for each effect of interest separately, a model incorporating as predictors the MEG ROIs that significantly differed between controls and patients was compared against a baseline model. This allowed identification of ROIs for that effect of interest that made the most significant contribution to discriminating between groups. A backwards step-wise regression method was used, based upon significance of the likelihood ratio, this being the proportional change in log-likelihood (reflecting the model's goodness-of-fit) if a predictor variable is removed from the model. The likelihood ratio is often multiplied by -2, termed '-2LL' as this approximates a chi-squared distribution, which is convenient for calculating significance levels. In this backwards stepwise procedure, variables that increased the -2LL with a significance level of less than .1 were removed.

Secondly, all those predictor variables from the above individual effect of interest models, those not removed in the previous step, were incorporated into a single model. A backwards step-wise procedure was again used in order to exclude any unnecessary variables and arrive at the most parsimonious possible solution. Sensitivity and specificity, effect size (Nagelkerke's R^2 - R^2_N, the difference in the proportion of variance explained by the full versus baseline model), goodness of fit (*Hosmer-Lemeshow:* χ^2), leverage values, residuals and tolerance measures were considered in order to assess the model's validity.

4.2 Results

4.2.1 Behavioural data

4.2.1.1 MEG task

The pAD group performed less well than controls on the MEG congruency task. Although all appeared to understand the task, some had difficulty in withholding their button-press responses until the cue to respond. As such trials were logged as incorrect this produced an overall reduction in task accuracy. As a result, all MEG trials were

included in analyses, unlike the control group where MEG data were examined only for correct responses.

4.2.1.2 Recall of MEG task items

50% (4 out of 8) of the pAD group freely recalled zero items. Others freely recalled 2, 3, 8 and 15 items. See *Figure 4.1a*. Only 7 of the 8 pAD patients were willing to participate in the cued recall task, of these, no patient recalled any incongruent item. Therefore total cued recall scores were comprised entirely from correctly recalled congruent items, ranging from 2.1% to 27.1% with a mean of 14.0% (SD=9.9%). As is clearly evident from *Figure 4.1b*, total cued recall scores were significantly lower in pAD patients than controls (control-*pAD: $t(7.20)=7.01$, $p<.001$*) and more variable (*Levene's $F=5.69$, $p=.023$*).

4.2.1.3 Neuropsychological test scores

We used pAD patients' most recent memory component score, which on average was obtained 74 days prior to the MEG task (SD=47 days). Patients' scores ranged from 5 to 17 out of the maximum possible score of 26 (M=12.8, SD=3.63), all were below the cut-off threshold according to age for 'normal' memory performance (2 standard deviations below the mean for age group of 23.4, as per Mioshi *et al.*, 2006). The distribution of scores is depicted in *Figure 4.1c*. In keeping with their diagnoses, pAD patients showed impaired performance across multiple domains, as assessed by ACE-R. Mean total ACE-R score (out of 100) was 70.2 (SD=8.17), with a highest score within the group of 83, see *Figure 4.1d*. This can be compared to a cut-off threshold of 88 which correctly identified 94% of pAD cases and correctly excluded 89% of non-demented control participants in the study of Mioshi *et al.* (2006).

4.2.1.4 Relationships between Behavioural Measures

There were significant positive correlations between all 3 behavioural memory measures (*Cued recall & Free recall: $r(7)=.829$, $p=.011$; Cued recall & ACE-R memory: $r(7)=.742$, $p=.028$; Free recall & ACE-R memory: $r(8)=.648$, $p=.041$*), despite floor effects present in the recall data. None of the memory measures significantly correlated with total ACE-R score, which is a composite of scores from multiple domains (*Total ACE-R & memory measures: all $r\leq.479$, $p>.11$*).

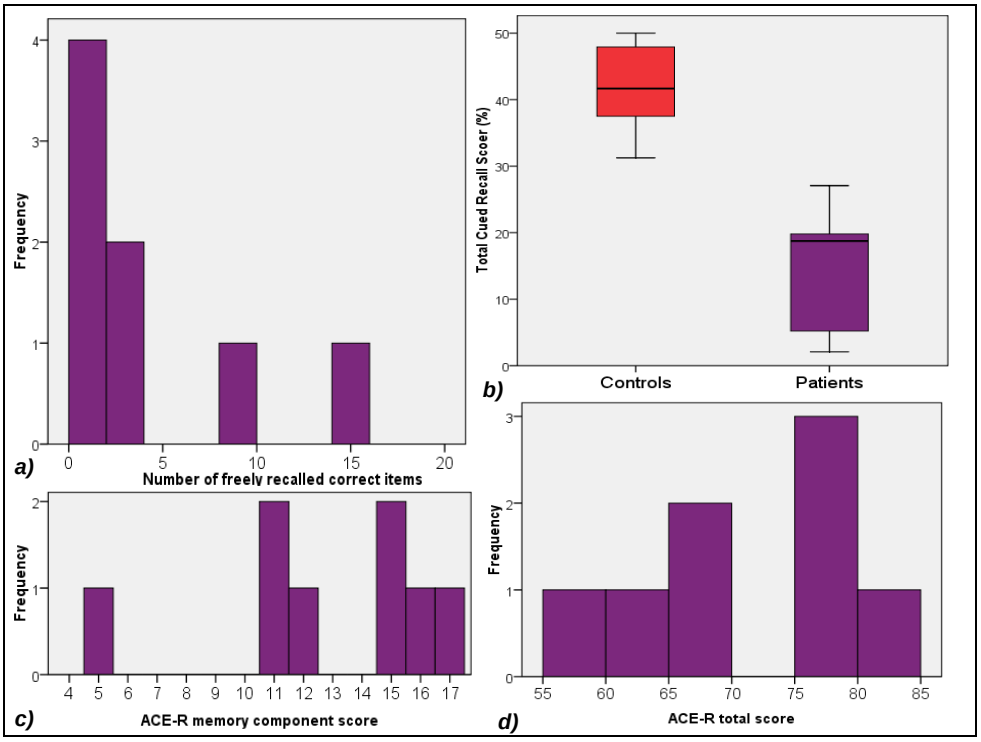


Figure 4.1: Behavioural measures of memory

a) Histogram depicting free recall performance in the patient group; b) Boxplots contrasting cued recall scores of patient and control groups. Error bars represent 95% confidence intervals; c) Histogram depicting ACE-R memory component scores in patient group; d) Histogram depicting total ACE-R scores in patient group.

4.2.2 Signal-to-Noise Ratio (SNR)

High SNR persisted in the pAD group, with means of 16.3 (4.80) and 22.9 (10.9) for magnetometers and gradiometers respectively. As with the control group, gradiometers had higher SNR than magnetometers (*Magnetometers-Gradiometers: Z=-2.10, sig.=.036*). SNR did not differ significantly between pAD and control groups (control-*pAD: Magnetometers: Z=-0.266, sig.>.7; Gradiometers: Z=-0.419, sig.>.6*).

4.2.3 N400m congruency effect

4.2.3.1 Magnetometers

FAL of the CE across the 400-600ms time window did not differ in patients relative to controls (control-*pAD: t(34)=0.211, p>.83*), although there were more extreme measures in both directions in the pAD group (see *Figure 4.4a*). As the time courses in *Figure 4.4b* illustrate, at the left fronto-temporal ROI (MEG021m), the pAD group response magnitude at initial presentation during the N400m time window was both increased for congruent items and reduced for incongruent items, relative to the control group. Patients demonstrated significantly reduced CE magnitude relative to controls at 3 of the 4 ROIs

(control-*pAD: MEG021m: t(34)=-1.95, p=.025; MEG122m: t(34)=1.85, p=.037; MEG194m: t(34)=1.95, p=.030*), see *Figures 4.4c-d*. These were included in later analyses (sections 4.2.7-8).

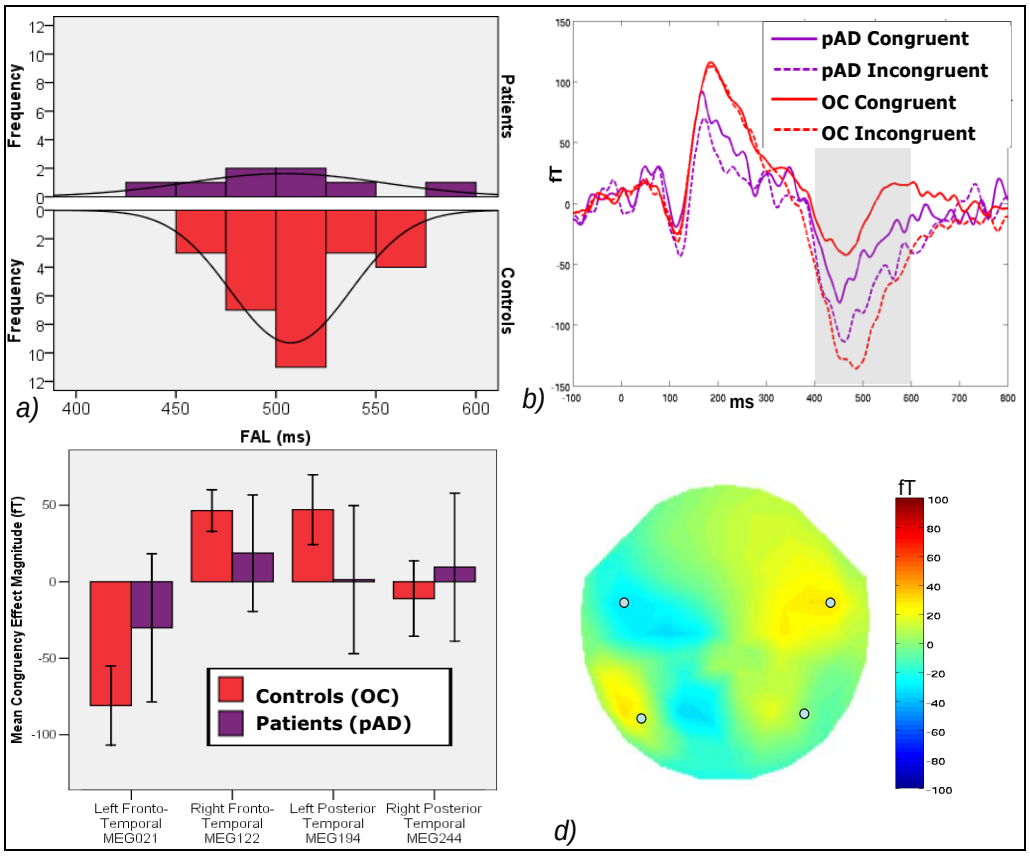


Figure 4.4: N400m Congruency Effect in Magnetometers

a) FAL according to group, from 400ms-600ms at MEG021m; b) Group average time courses for original conditions at MEG021m. Shaded area indicates time window of interest. c) Mean CE magnitude at each ROI from 400-600ms according to group. Error bars represent 95% confidence intervals; d) pAD group mean CE topography, 400-600ms. ROIs are highlighted.

4.2.3.2 Gradiometers

Control and pAD groups did not differ in CE FAL at the controls' maximal ROI MEG161g (*t(34)=-0.978, p>.33*), see *Figure 4.5a*. While a CE was evident in the pAD group average time course and topography (*Figure 4.5c-d*), it was virtually non-existent at this ROI (MEG161g) in five out of the eight patients tested (*Figure 4.5b*). Nonetheless, the trend for reduced CE magnitude in the pAD group was only marginally significant (control-*pAD: t(34)=1.67, p=.053*), most probably due to one outlier within the patient group (*Figures 4.5b&e*). ROI MEG161g was retained for further examination in sections 4.2.7-8. No group differences reached significance at any other ROI (control-*pAD: all t(34)<1.50, p>.07*).

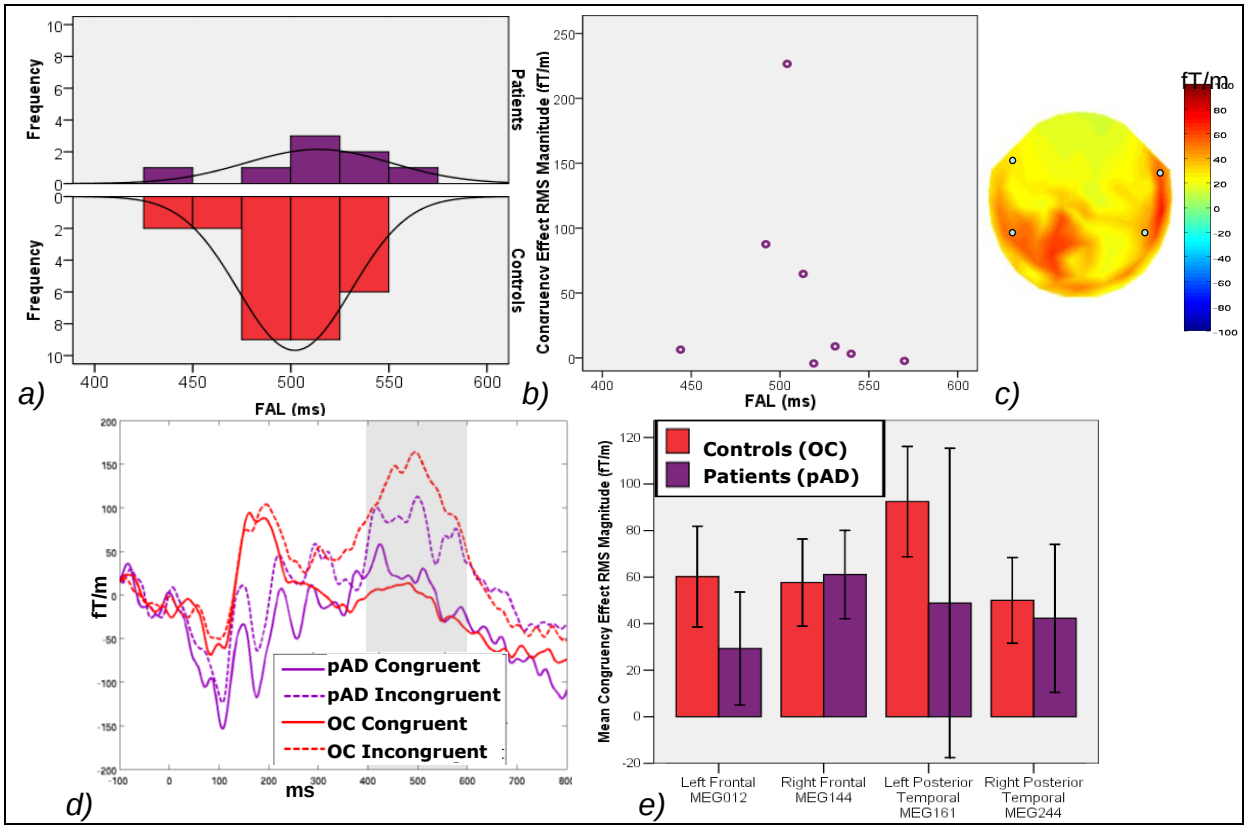


Figure 4.5: N400m Congruency Effect in Gradiometers

a) FAL according to group, from 400ms-600ms at ROI MEG161g; b) Scatterplot depicting relationship of FAL with RMS magnitude of effect within the pAD group at ROI MEG161g; c) PAD group mean RMS of the difference topography in gradiometers, 400-600ms. ROIs are highlighted. d) Group average time courses for original conditions in unrectified left posterior temporal gradiometer MEG161(2). Shaded area indicates time window of interest. e) Mean effect magnitude at each ROI from 400-600ms according to group. Error bars represent 95% confidence intervals.

4.2.4 N400m incongruent repetition effect

4.2.4.1 Magnetometers

FAL of the IRE did not significantly differ between patients and controls (control-*pAD: MEG021m: t(32)=1.17, p=.25*), see *Figure 4.6a*. *Figures 4.6b-c* show absent or reversed direction of the IRE in the pAD group at several ROIs. However, large intra-group variability meant that the majority of between-group differences did not reach significance. Nonetheless, there was a highly significant group difference at the right fronto-temporal ROI, MEG132m (control-*pAD: t(34)=2.69, p=.006*). The absence of an IRE was evident in the pAD group average time course at this ROI, see *Figure 4.6d*. This ROI was retained for further analyses.

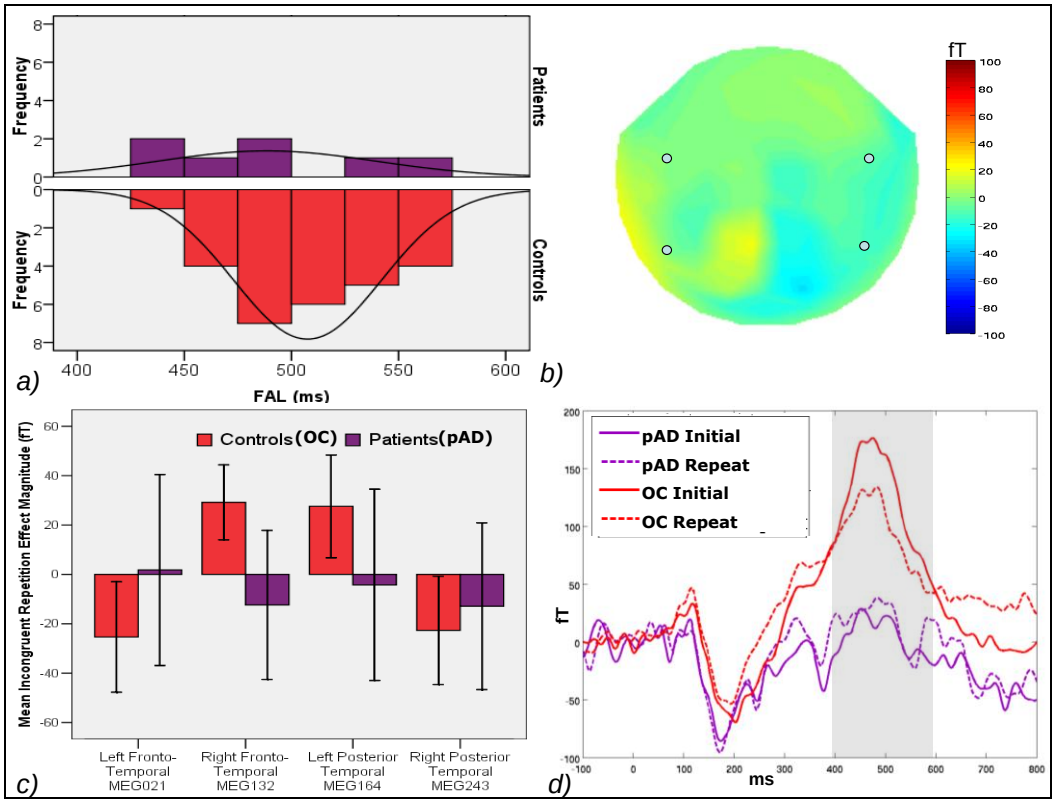


Figure 4.6: N400m Incongruent Repetition Effect Magnitude in Magnetometers
a) FAL according to group, from 400ms-600ms at MEG132m; b) PAD group mean topography for effect in magnetometers from 400-600ms. ROIs are highlighted; c) Mean effect magnitude at each ROI according to group. Error bars represent 95% confidence intervals. d) Group average time courses for original conditions at MEG132m. Shaded area indicates time window of interest.

4.2.4.2 Gradiometers

FAL did not significantly differ between the patient and control group (control-*pAD: t(34)=1.42, p>.16*), see *Figure 4.7a*. Although the pAD group mean topography (*Figure 4.7d*) suggested a smaller magnitude of IRE on average than for the control group (*Figure 3.7d*), there were no significant group differences at any ROI (see *Figure 4.7b* for an example of group average time courses) and large variance in measurements within both groups (see *Figure 4.7c*).

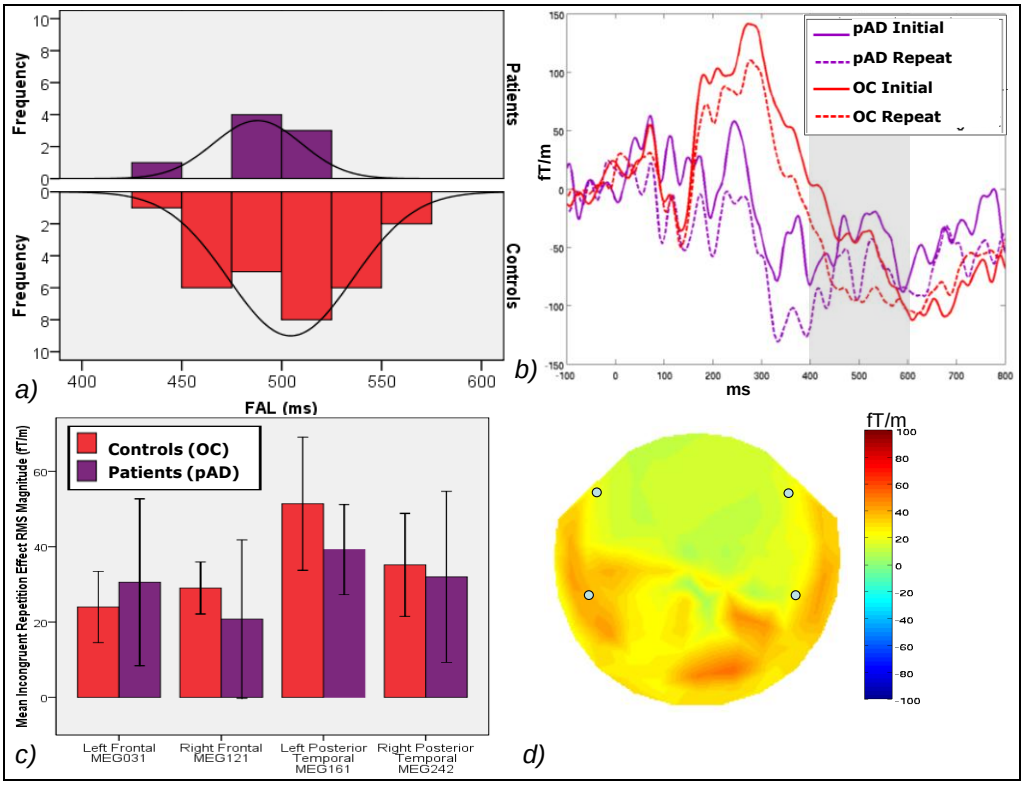


Figure 4.7: N400m Incongruent Repetition Effect in gradiometers

a) FAL according to group, from 400ms-600ms at MEG161g; b) Group average time courses for original conditions at unrectified left posterior temporal gradiometer MEG161(3). Shaded area indicates time window of interest. c) Mean incongruent repetition effect RMS magnitude at each ROI according to group. Error bars represent 95% confidence intervals. d) PAD group mean RMS of difference topography for effect in gradiometers, 400-600ms. ROIs are highlighted.

4.2.5 P600m congruent repetition effect

4.2.5.1 Magnetometers

FAL of the CRE did not differ between patients and controls (control-*pAD: MEG173m: t(33)=-0.888, p*>.38), Figure *4.8a*, though there was a suggestion of a delayed CRE in the pAD group. At the left fronto-temporal ROI (MEG021m), significantly reduced CRE magnitude was evident within the pAD group relative to controls (control-*pAD: MEG021m: t(34)=1.95, p=.030*), see *Figure 4.8b-d*; this ROI was retained for further analyses.

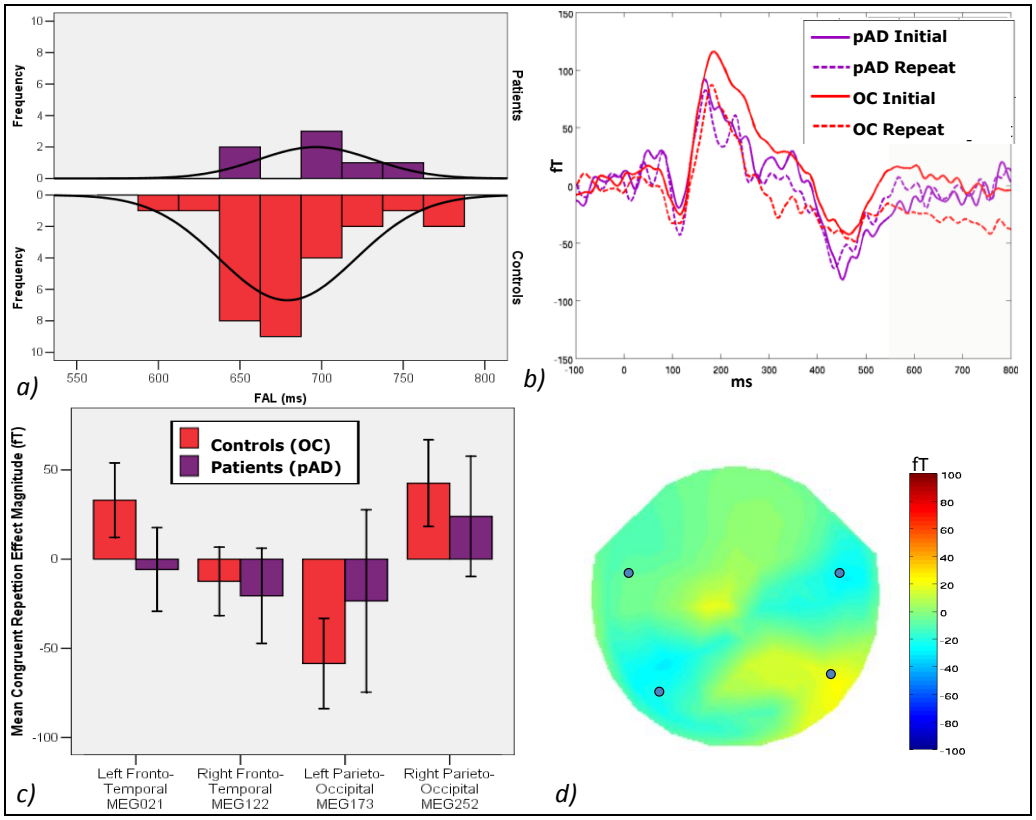


Figure 4.8: P600m Congruent Repetition Effect in Magnetometers

a) FAL according to group, from 550ms-800ms at MEG173m; b) Group average time courses for original conditions at left fronto-temporal ROI MEG021m. Shaded area indicates time window of interest. c) Bar chart illustrating effect magnitude at each ROI according to group. Error bars represent 95% confidence intervals. d) Probable AD patient group mean topography for effect in magnetometers, 550-800ms. ROIs are highlighted.

4.2.5.2 Gradiometers

CRE FAL in gradiometers was prolonged by a mean of 27ms (SE=14.7ms) in the pAD relative to control group at the left posterior temporal ROI, MEG164g (*pAD-control: t(34)=1.81, p=.040*). This was perhaps due to a prominent repetition effect being present throughout the epoch from 200ms in the control group only (whereas the diminished effect did not become evident until around 550ms in the patient group), see *Figures 4.9a-b*. Significantly reduced CRE magnitude in the pAD group relative to controls was evident at both (posterior temporal) ROIs, MEG164g and MEG242g (control-*pAD: MEG164g: t(34)=2.29, p=.015; MEG242g: t(34)=1.69, p=.050*), see *Figures 4.9b-d*. Both ROIs were retained for further analyses.

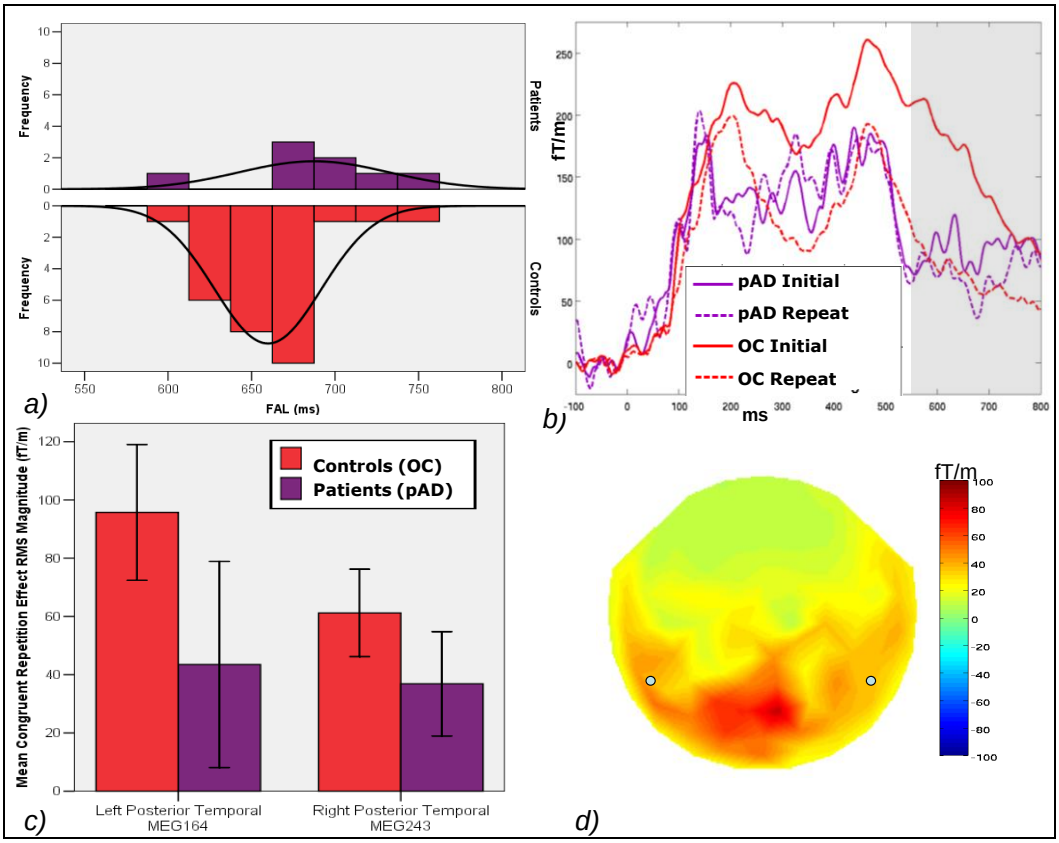


Figure 4.9: Congruent Repetition Effect in Gradiometers

a) FAL according to group, from 550ms-800ms at MEG164g; b) Group average time courses for RMS of original conditions at left posterior temporal ROI MEG164g. Shaded area indicates time window of interest. c) Bar chart illustrating effect magnitude at each ROI according to group. Error bars represent 95% confidence intervals. d) Patient group mean topography for RMS of the effect in gradiometers, 550-800ms. ROIs are highlighted.

4.2.6 Early repetition effect

4.2.6.1 Magnetometers

FAL of the RE did not significantly differ between patients and controls (*pAD-control: MEG151m: t(33)=1.24, p>.22*), see *Figure 4.10a*. As depicted in *Figures 4.10b*-d, magnitude of the RE was significantly reduced at the left mid-temporal ROI (MEG151m) in patients relative to controls (control-*pAD: t(34)=2.13, p=.040*) and pAD group average time courses suggested severely diminished magnitude during the 200-400ms time window for both original conditions (*Figure 4.10b*). Indeed, initial conditions were of significantly smaller magnitude in patients than controls at this ROI (control-*pAD: t(34)=2.61, p=.013*). This ROI was included in subsequent analyses.

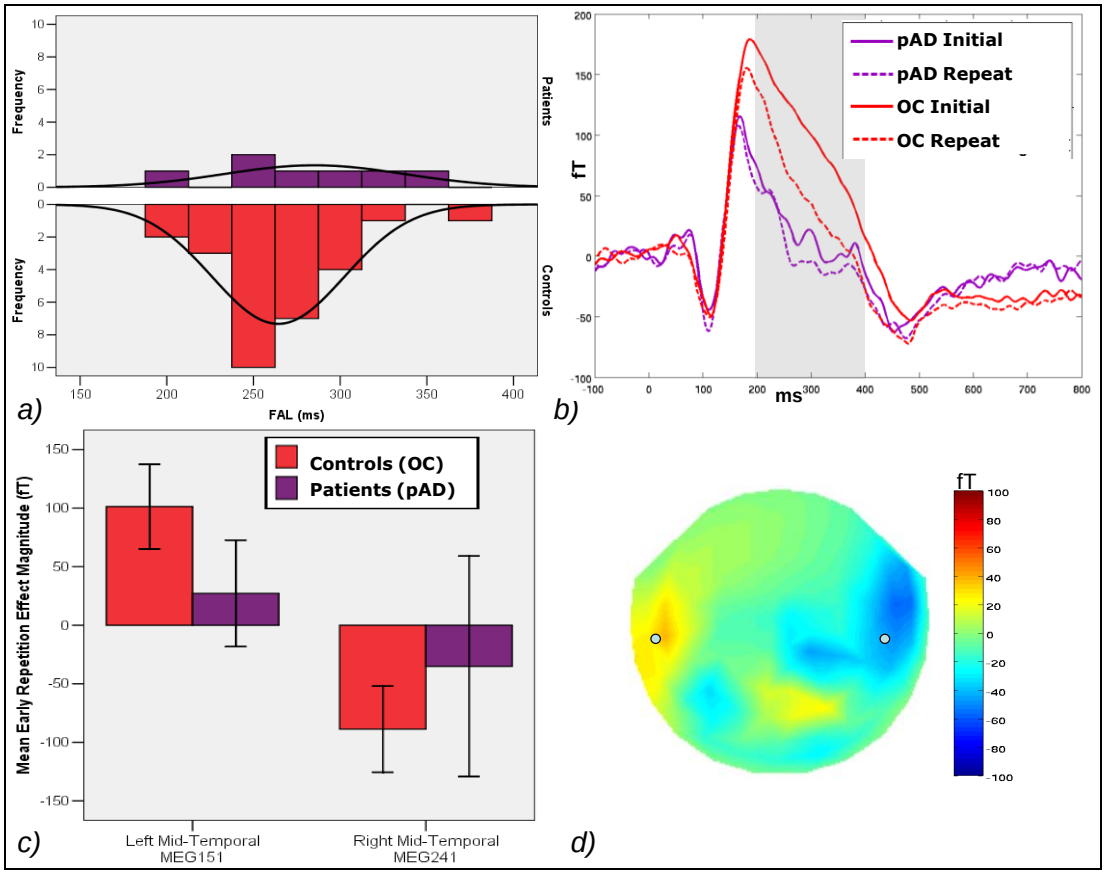


Figure 4.10: Early Repetition Effect in Magnetometers

a) FAL according to group, from 150ms-400ms at MEG151m; b) Group average time courses for original conditions at left mid-temporal ROI MEG151m. Shaded area indicates time window of interest; c) Mean effect magnitude at each ROI from 200-400ms according to group. Error bars represent 95% confidence intervals; d) PAD group mean topography for effect in magnetometers, 200-400ms. ROIs are highlighted.

4.2.6.2 Gradiometers

RE latency did not significantly differ between pAD and control groups (*control-pAD: t(21.9)=1.21, p>.23*), see *Figure 4.11a*. As observed in magnetometers, the pAD group average time courses suggested a decrement of the response to initial presentation of items during the time window of interest (*Figure 4.11b*), but these group differences fell short of significance (control-*pAD: all t(34)<1.83, p>.07*). Magnitude of the RE was greatly reduced at three of the four gradiometer ROIs (right frontal and both parieto-occipital ROIs), as depicted in *Figures 4.11c-d* (control-*pAD: MEG092g: t(34)=2.14, p=.040; MEG173g: t(27.3)=3.55, p=.001; MEG243g: t(34)=2.56, p=.015*), all of which were included in later analyses.

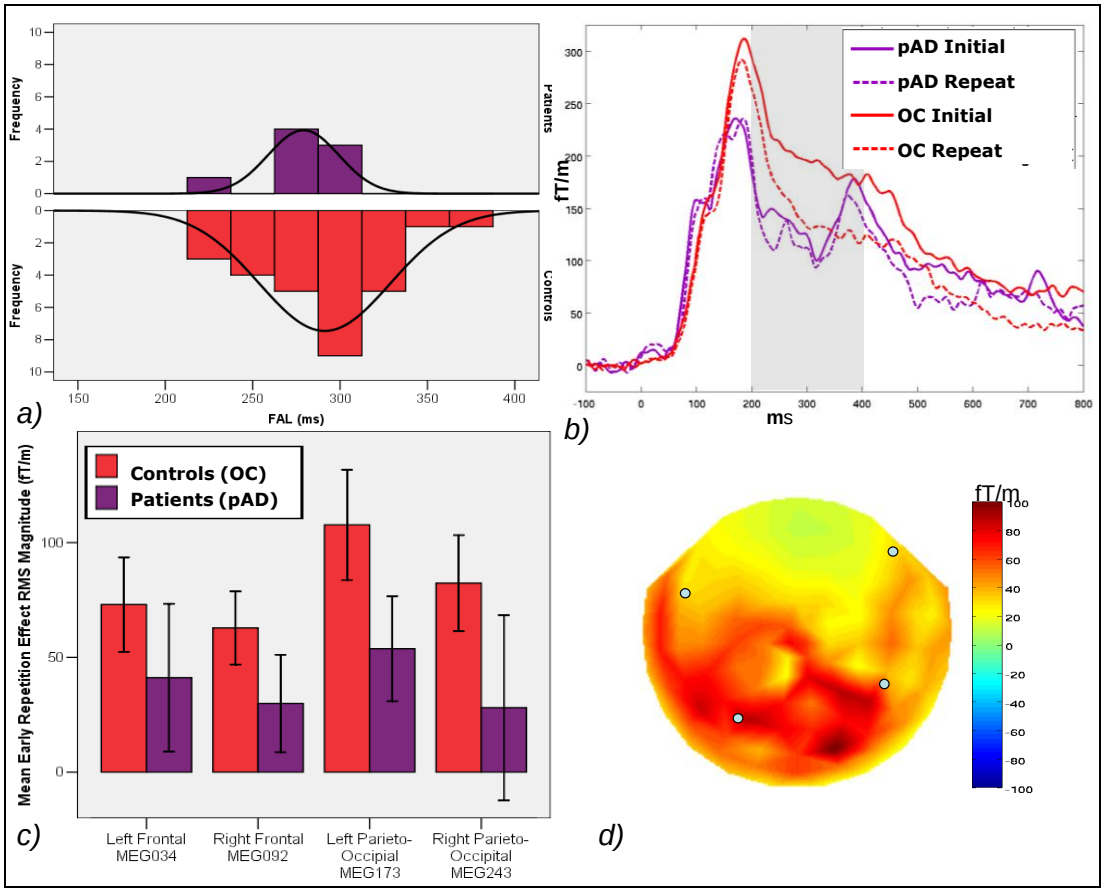


Figure 4.11: Early Repetition Effect in Gradiometers

a) FAL according to group, from 150ms-400ms at MEG173g; b) Group average time courses for RMS of original conditions at left parieto-occipital ROI MEG173g. Shaded area indicates time window of interest; c) Mean RE magnitude at each ROI according to group. Error bars represent 95% confidence intervals; d) PAD group mean topography for RMS of the effect in gradiometers, 200-400ms. ROIs are highlighted.

4.2.7 10th percentile cut-offs

Table 4.1 lists the 10th percentile cut-off thresholds for measures that significantly differed between groups and the sensitivity of these thresholds to pAD group membership. None of these measures offered individual sensitivity above 62.5%. However each effect of interest had at least one ROI that demonstrated sensitivity of above or equal to 50%.

The ROI that conferred maximal sensitivity for each effect of interest (highlighted in *Table 4.1* above) was selected and the total number of 'low' (below 10th percentile) measures from these 4 variables was computed for each individual. 78.6% (22/28) of controls had no low measures, 17.9% (5/28) had just one low measure, and the remaining control group member had 2 low measures. In contrast, 75% of pAD patients (6/8) had low measures for 2 or more of the 4 variables. However one pAD group member had no low measures and the other had only one (see *Figure 4.12*). The requirement that, to be

considered 'healthy', an individual should have no more than one 'low' measure, yielded highest accuracy and gave sensitivity and specificity of 75% and 96.4% respectively. Higher sensitivity was obtained by requiring no low measures (87.5%), but specificity fell to 78.6%.

Table 4.1 - MEG effects differing between pAD and control groups
Cut-off threshold is control group 10th percentile, which conferred 92.9% specificity. The most sensitive ROI for each effect of interest is highlighted.

Effect of interest	Location	ROI	Cut-off	Sensitivity
Congruency Effect	Left Fronto-Temporal Magnetometer	MEG021m (CE021m)	(>)104.8fT	25% (2/8)
Congruency Effect	Right Fronto-Temporal Magnetometer	MEG122m (CE122m)	5.51fT	50% (4/8)
Congruency Effect	Left Posterior Temporal Magnetometer	MEG194m (CE194m)	-50.1fT	12.5% (1/8)
Congruency Effect	Left Posterior Temporal Gradiometer	MEG161g (CE161g)	24.4fT/m	62.5% (5/8)
Incongruent Repetition Effect	Right Fronto-Temporal Magnetometer	MEG132m (IRE132m)	-5.79fT	50% (4/8)
Congruent Repetition Effect	Left Fronto-Temporal Magnetometer	MEG021m (CRE021m)	-37.5fT	25% (2/8)
Congruent Repetition Effect	Left Posterior Temporal Gradiometer	MEG164g (CRE164g)	25.7fT/m	50% (4/8)
Congruent Repetition Effect	Right Posterior Temporal Gradiometer	MEG242g (CRE242g)	11.8fT/m	13% (1/8)
Early Repetition Effect	Left Mid-Temporal Magnetometer	MEG151m (RE151m)	-30.6fT	12.5% (1/8)
Early Repetition Effect	Right Frontal Gradiometer	MEG092g (RE092g)	24.6fT/m	50% (4/8)
Early Repetition Effect	Left Parieto-Occipital Gradiometer	MEG173g (RE173g)	32.1fT/m	25% (2/8)
Early Repetition Effect	Right Parieto-Occipital Gradiometer	MEG243g (RE243g)	5.29fT/m	37.5% (3/8)

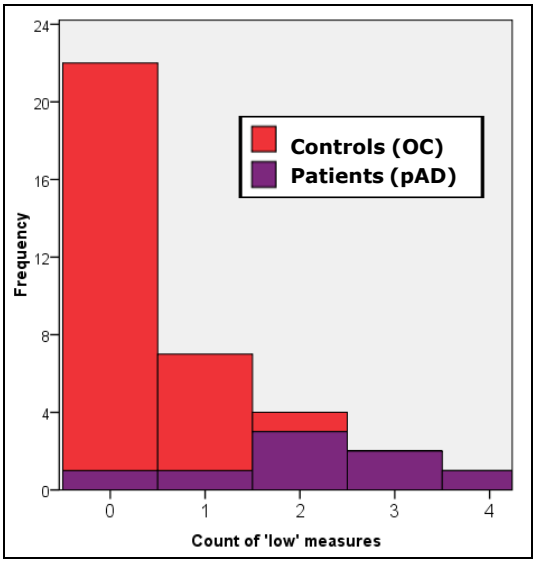


Figure 4.12: Count of 'low' MEG measures according to group

4.2.8 Logistic Regression

4.2.8.1 Congruency Effect

Four ROIs for the CE were identified as differing between patients and controls, as listed in *Table 4.1*. When compared against a baseline model using a backwards stepwise regression procedure, 2 variables were retained. These were right fronto-temporal and left posterior temporal magnetometer ROIs (CE122m and CE194m). This model (see *Table 4.2*) was a significant improvement upon the baseline model (*-2LL=29.2, p=.011*), with an effect size of .337 and demonstrated 92.9% (26/28) specificity but only 50% (4/8) sensitivity to pAD.

4.2.8.2 Incongruent Repetition Effect

Only a single ROI for the IRE was identified as significantly differing between patients and controls: the right fronto-temporal magnetometer ROI IRE132m. The model incorporating this variable as predictor (*Table 4.2*) was a significant improvement over the baseline model (*-2LL=30.9, p=.007*), with an effect size of .280, demonstrating 92.9% (26/28) specificity and 62.5% (5/8) sensitivity to pAD.

4.2.8.3 Congruent Repetition Effect

Three ROIs for CRE magnitude, as listed in *Table 4.1*, were used as predictor variables for this analysis. Only the left posterior temporal gradiometer ROI, CRE164g was retained as part of a model (*-2LL=32.1, p=.014*; see *Table 4.2*), with an effect size of

.238. This model demonstrated 100% (28/28) specificity and 75% (6/8) sensitivity to pAD.

Table 4.2: MEG LR predictors for pAD/control classification, modelled for each effect of interest separately.

Effect of interest modelled	ROI	Beta (SE)	Change in -2LL	Significance
Congruency Effect	Right fronto-temporal magnetometer CE122m	-1.02 (0.50)	-5.17	.023
	Left posterior temporal magnetometer CE194m	-1.22 (0.59)	-5.49	.019
	Constant	-2.22 (0.716)		.002
Incongruent Repetition Effect	Right front-temporal magnetometer IRE132m	-1.25 (0.54)	-7.27	.007
	Constant	-1.93 (0.603)		.001
Congruent Repetition Effect	Left posterior temporal gradiometer CRE164g	-1.36 (0.67)	-6.08	.014
	Constant	-1.94 (0.660)		.003
Early Repetition Effect	Left parieto-occipital gradiometer RE173g	-1.84 (1.07)	-5.20	.023
	Right parieto-occipital gradiometer RE242g	-1.44 (0.70)	-6.06	.014
	Constant	-3.25 (1.29)		.012

**For small group sizes such as here, SE may be over-estimated.*

4.2.8.4 Early Repetition Effect

Four ROIs, 3 gradiometers and 1 magnetometer, for the RE significantly differed between controls and patients. The model (see *Table 4.2*) retained 2 of these, left and right parieto-occipital gradiometer ROIs RE173g and RE242g, (*-2LL=25.8, p=.002*), with an effect size of .444, demonstrating 89.3% (25/28) specificity and 62.5% (5/8) sensitivity to pAD.

4.2.8.5 Combination of all significant contrast effects

The variables retained for each effect of interest in the logistic regression analyses described above are listed in *Table 4.2*. Again using a backwards stepwise logistic regression procedure, whereby variables were removed if they did not significantly reduce the likelihood ratio, 4 of these 6 variables were retained as significant predictors; model predictors are listed in *Table 4.3*.

The resultant model demonstrated 100% (28/28) specificity and 87.5% (7/8) sensitivity to the diagnosis of probable AD, a significant improvement in discriminability from the baseline model (*-2LL=13.5, p<.001*), with an effect size of .759 and a satisfactory goodness of fit ($\chi^2(7)=9.12, p>.24$). The effect size for this model was far greater than that for any contrast modelled individually.

Regression coefficients for all predictors were in the negative direction, indicating that as they became smaller or more negative, the likelihood of a diagnosis of pAD increased. As predictors were standardised before being entered into the model, their relative extent of influence was directly comparable and ranged between -2.12 and -3.14, demonstrating that no individual predictor dominated the model. There was no evidence for multicollinearity within the model, with all tolerance values at or above 0.735 and variance inflation factor (VIF) at or below 1.33. Notably standard errors for some predictors were quite large. This may be explicable as a result of over-inflated standard errors which are a feature of logistic regression models based upon small samples such as this, however, it could be a sign that the regression co-efficients were unreliable, perhaps due to over-fitting.

The single misclassified case, a false negative, was an outlier with a standardised residual of 5.75. This individual had a Cook's value of 2.71, (indicating potential undue influence over the solution), however all other individuals (for whom the model fitted) had Cook's values of less than one, indicating no undue influence over the model. The same patient who was misclassified by this model was the sole member of the patient group who had no low measures using the 10th percentile cut-off thresholds described in

the previous section. Although this individual had great difficulty in keeping still during the MEG task, resulting in relatively few trials (because of movement-related artefacts) being incorporated into his evoked responses, SNR was acceptable at 9.99 and 9.87 for magnetometers and gradiometers respectively.

Table 4.3: MEG predictors of pAD/control classification in model combining all effects of interest

Effect of interest (ROI)	Location	Beta (SE)	Change in -2LL	Significance
Congruency Effect (CE194m)	Left Posterior Temporal Magnetometer	-2.12 (1.04)	-6.75	.009
Congruent Repetition Effect (CRE164g)	Left Posterior Temporal Gradiometer	-3.14 (1.60)	-8.59	.003
Early Repetition Effect (RE173g)	Left Parieto-Occipital Gradiometer	-2.63 (1.81)	-5.37	.021
Early Repetition Effect (RE242g)	Right Parieto-Occipital Gradiometer	-2.60 (1.14)	-10.4	.001
	Constant	-7.29 (2.89)		.012

**Model $\chi^2(4)=24.7$, $p<.001$; $R^2_N=.759$; Overall accuracy=97.2%.*
For small group sizes such as here, SE may be over-estimated.

4.3 Chapter Summary

MEG measures at ROIs defined in the previous chapter were compared between pAD and older control groups (Aim 1). Group differences were utilised to define a MEG-based metric able to discriminate between the groups (Aim 2). While the selection of the specific MEG measures on the basis of reliable group differences biases the classification methods (logistic regression and 10th percentile thresholding) towards above-chance performance, the main (unbiased) test of this classification metric will be the larger patient group in the next chapter.

Behaviourally, some of the group of pAD patients performed less well than controls on the MEG congruency task, therefore to ensure reasonable SNR, data from all

trials were incorporated into analyses for this group. Free recall performance was at floor in the pAD group, and all had previously performed below the normal cut-off threshold for age in terms of total score and memory component of the ACE-R. The pAD group performed above floor on the subsequent cued recall task, though still well below the control group.

4.3.1 Group differences (Aim 1)

We predicted diminished effect magnitudes for the pAD group relative to patients for all effects of interest, except the early repetition effect for which we had no clear expectations. Measures upon which control and pAD groups significantly differed are summarised below. These identified ROIs were used for further analyses that aimed to uncover a function useful in classifying members of the two groups, the results of which were described in sections 4.2.7 and 4.2.8 and are summarised in section 4.3.2.

4.3.1.1 N400m congruency effect

The CE was reduced or absent in several pAD patients, overall there were no significant group latency differences. Significant group differences in effect magnitude were identified at multiple magnetometer ROIs, whilst the presence of a single outlier in the patient data opposed an overall group difference that fell just short of significance at the left posterior temporal gradiometer ROI (CE161g). Nonetheless, given that the effect appeared absent at this ROI in a large proportion of patient cases (5 out of 8), this ROI was also retained for later use.

4.3.1.2 N400m incongruent repetition effect

Variability in IRE magnitude was high in both groups, therefore despite very low and reversed polarity pAD group average responses in magnetometers, group differences attained significance at only 1 magnetometer ROI and no significant group differences were identified in gradiometers.

4.3.1.3 P600m congruent repetition effect

Magnitude of this effect was reduced in the pAD relative to control group in both sensor types, most markedly at left posterior temporal gradiometer ROI CRE164g and left fronto-temporal magnetometer ROI CRE021m. Effect latency was delayed in patients

relative to controls at the gradiometer ROI, but it was not deemed necessary to adjust the time window due to a prolonged repetition effect in the controls.

4.3.1.4 Early repetition effect

The RE detected by both MEG sensor types was greatly diminished bilaterally in pAD patients relative to controls, which also tended to be the case to a lesser extent for underlying components upon initial as well as repeat presentations during the time window of interest, as well as the preceding peak (~170ms). Latencies did not differ between groups.

4.3.2 Predictive value of identified MEG contrasts (Aim 2)

4.3.2.1 10th percentile cut-offs

We replicated the method applied in an EEG study (Olichney, et al., 2006), whereby 10th percentile cut-off thresholds were taken for measures identified in the above step. The ROI offering the maximal sensitivity to pAD using this threshold was chosen for each effect of interest, giving a total of 4 measures, and the numbers of low measures out of these 4 were summed. Requiring no more than one low measure to be considered 'healthy' conferred highest overall accuracy, with 75% sensitivity and 96.4% specificity, whereas a requirement for no low measures was more sensitive but less accurate overall (87.5% sensitivity and 78.6% specificity).

4.3.2.2 Logistic regression

To attain the most parsimonious solution, we initially considered separately for each effect of interest all measures of effect magnitude that significantly differed between groups and used a backwards step-wise procedure to remove all predictor variables that did not significantly improve the model accuracy. In the second step, we applied the same procedure to combine all variables retained in step one. Four predictor variables were retained in the final combined model: one CE predictor (CE194m), one CRE predictor (CRE164g), and two RE predictors (RE173g and RE242g). The formula by which probability of having a diagnosis of probable AD can be derived from these variables is found below. This conferred sensitivity at 87.5% and specificity at 100%.

Formula 4.1: Equation for probability of diagnosis of Alzheimer's-type dementia

$$y_i = -7.29 - (2.12 \times CE194m_i) - (3.14 \times CRE164g_i) - (2.63 \times RE173g_i) - (2.60 \times RE242g_i)$$

Predictor variable measurement units are z-scores

Chapter 5
Active memory paradigm in memory clinic patients

The following chapter applied the same active MEG memory paradigm and metrics devised in the previous chapter to a group of individuals, similar in age to those in the pAD and control groups, who presented at a hospital memory clinic with complaints of memory loss, but whose behavioural neuropsychological scores had a large range that overlapped with healthy performance (henceforth, the memory clinic, MC group). The MEG metrics were used to predict which of these individuals are likely to have incipient dementia (mild cognitive impairment, henceforth the MCI subgroup), rather than problems associated with normal ageing or affective disorders (henceforth the "worried well", or WW group). As the final clinical diagnosis of these patients was not know at the time of MEG testing (but might be available in future, via longitudinal follow-up to identify those individuals that go on to be diagnosed with pAD), we attempted to validate the MEG LR model and 10th percentile metric against the best-guess predictions of an experienced consultant clinical neurologist, who had access to the usual clinical data (including neuropsychological scores), but not the MEG or behavioural data from the present paradigm.

Aims & predictions

Aim 1. Describe MEG & behavioural measures in MC relative to pAD & control groups

To give an impression of the data distribution within the MC group as a whole, MEG and behavioural measures were contrasted between the MC group and pAD and control groups. It was anticipated that MC group averages would be intermediate to those of the other groups and broader in distribution, given the expected pathological heterogeneity of this group. As those classified MCI by the clinician in the current MC group were considered to have incipient dementia, we expected these cases to show more marked MEG changes than the WW cases. However, the effects examined here have not been previously studied in individuals suffering from affective disorders, who may have comprised a proportion of the WW cases; therefore the impact of such cases upon the MEG effects cannot be anticipated.

Prior EEG studies found that CRE magnitude was diminished and latency of the IRE and CE delayed in an MCI group relative to controls (Olichney, et al., 2002);

furthermore reduced IRE and/or CRE magnitude was predictive of those who subsequently converted to Alzheimer's disease (Olichney, Morris, et al., 2002; Olichney, Taylor, Gatherwright, et al., 2008).

The finding of a reduced RE in the pAD group in Chapter 4 was likely pre-semantic in origin, given the relatively early time window of the effect and its indifference to semantic congruency. Given the absence of an RE in the pAD group, we predicted some decrement in RE magnitude within the MC group.

Aim 2. Examine how MEG measures vary according to behavioural performance

It was predicted that MC patients with lower behavioural performance, particularly on recall for MEG task items and on ACE-R total score and its memory sub-component, would demonstrate reduced and/or delayed MEG responses for each effect of interest, given that all were associated with memory performance of the young control group in chapter 2. Whilst the cued recall measure tests memory for the specific items encountered during the MEG task relies primarily on long-term episodic memory, supported by semantic associations (Nobel & Shiffrin, 2001), the ACE-R is a composite, reflecting multiple aspects of cognitive function. All ACE-R subcomponents, except that assessing visuo-spatial ability, show a decrement in patients with incipient dementia relative to controls (Mioshi, et al., 2006), whilst impaired performance limited to memory and (primarily phonological) fluency domains, with a total score of 88 or above, differentiates affective disorders (e.g. WW subgroup) from incipient dementia (e.g. MCI subgroup, Dudas, Berrios, et al., 2005). Sensitivity to impairment in domains other than memory would be a good indicator that a MEG measure or model is attuned to neurophysiological processing deficits that distinguish depression from incipient dementia.

Aim 3. Assess utility of MEG & behavioural measures in predicting clinician's provisional diagnosis

In an effort to circumvent circularity of using the control/pAD group comparison to both define ROIs that differed between these groups and to assess these measures' sensitivity/specificity, we assessed the utility of the MEG measures within this independent dataset of MC patients in predicting the expert clinician's 'best guess' opinion, made in the context of the available clinical information. The caveat here was that individuals classified as MCI by the clinician were those who he felt had highest

likelihood of progression to dementia, but he emphasised that no definitive diagnoses were available (at the time of writing).

To achieve this aim, we established the 'MCI versus WW' classification accuracy of the various behavioural measures, MEG metrics and individual MEG measures identified in chapter 4 as differentiating pAD from control individuals. Finally, to gauge whether MEG measures added additional predictive ability to the behavioural data, we ran a backwards step-wise LR procedure and assessed if the addition of MEG measures to the most useful standardised behavioural predictor variables improved model accuracy.

5.1 Method

5.1.1 Participants

30 individuals (15 males) who presented at a local hospital memory clinic with complaints of recent memory decline, volunteered to participate in the study after receiving an invitation from a neurologist. The experimenter was blind to participants' provisional diagnoses at the time of testing and these were subsequently provided by the neurologist, who based his classifications upon the usual clinical data, that is, ACE-R scores and a clinical interview with the patient, occasionally a clinical MRI scan was also conducted. Eight participants constituted the MCI sub-group and the remainder were classified as WW. All but two participants were right-handed (one was left-handed, the other ambidextrous) and ranged in age from 56 to 76 years with a mean age of 67.0 years (SD=5.5years). Age did not significantly differ between MC and control (control-*MC: t(56)=1.25, p>.21*) or pAD groups (*MC-pAD: t(36)=1.75, p>.08*). Patients' participation in this study was approved by a local NHS regional ethics committee (LREC code: 08/H0306/68). All gave informed consent. They were unpaid for their participation but received reimbursement of travel expenses and refreshments during their visits.

As part of standard procedure, MC patients had undertaken the ACE-R, during their visit(s) to the memory clinic prior to participation in the current study. In cases where patients had completed the test on more than one occasion, we used the score from their most recent assessment prior to participating in the current study.

5.1.2 Procedure

The MEG active memory task and procedure were identical to those for the pAD group. As for the pAD and control groups, EEG data were consulted only informally and are not

reported further here. During subsequent behavioural testing, the group performed both free-recall and then cued recall.

5.1.3 Analysis approach

Pre-processing of MEG data and computation of SNR were identical to that used for other groups' data. As in the previous chapter, FAL and magnitude were computed in the same manner and for the same ROIs that were defined in chapter 3. Computation and comparisons of SNR were conducted as in previous chapters.

5.1.3.1 Comparison of behavioural and MEG measures of MC group with control and pAD groups

T-tests between the MC and pAD/control groups were made for measures of recall for MEG task items and for ACE-R total score and sub-components. Due to tendencies for floor / ceiling effects in some groups, non-parametric comparisons were used (Mann-Whitney test) for free-recall and all ACE-R sub-components. Where the control group was entirely at ceiling, formal statistical comparisons were not conducted. Pair-wise comparisons of magnitude and FAL were made between the MC and other groups in the same manner as the control-pAD contrasts in chapter 4.

5.1.3.2 Examination of relationships between MEG measures and behaviour

Within the MC group, correlation coefficients were computed between each behavioural measure and MEG ROIs and metrics defined in chapter 4 as sensitive to pAD. Spearman correlations were used for comparisons that involved the MEG 10^{th} percentile metric (due to the ordinal nature of the data), or ACE-R attention/orientation or visuo-spatial sub-components (due to limited range within these measures). Pearson correlation coefficients were calculated for all others. Correction for multiple comparisons was applied to account for the ACE-R total being comprised of the sum of the other ACE-R metrics, such that the alpha value was divided by a factor of 2 for each ACE-R measure; the same adjustment was applied for comparisons involving cued and free recall of the MEG task items. Additional correction was made when more than one ROI was tested for a particular effect of interest, with alpha value divided by the number of ROIs. Further correction was not applied for comparisons of different effects of interest or metrics, as we were interested to see how the relationships with behaviour differed amongst these measures. Likewise, we did not further correct for comparisons of MEG task item recall

versus ACE-R scores, as we wished to assess how relationships with MEG task-related memory measures differed from those of standardised assessments.

5.1.3.3 Sensitivity of MEG and behavioural measures to clinician's opinion

With the clinician's opinion as the state variable, Receiver Operating Characteristic (ROC) curves were constructed for behavioural and MEG measures. The ROC curve for a measure graphically represents the trade-off of true positive and false positive rates for every possible cut-off threshold. Optimal criterions were defined for MCI/WW classification as those that maximised sensitivity while maintaining a specificity of at least 50%. Deviation of the area under the ROC curve (AUC) from 0.5 (equivalent to 'chance') was used to establish whether each measure had significant sensitivity to the diagnosis of MCI. Significance was established using a non-parametric method equivalent to the Mann-Whitney U-statistic (DeLong, DeLong, & Clarke-Pearson, 1988).

5.1.3.4 Combined MEG / neuropsychology LR model for clinician's opinion

Logistic regression analysis with clinician's diagnosis (MCI or WW) as the dependent categorical variable was performed against the baseline model in a similar manner as for the control/pAD LR model in chapter 4, incorporating all ROIs that had significantly differed between control and pAD groups. Models were constructed first for each effect of interest separately, then all ROIs that were retained as predictor variables in the effect of interest models were combined into a final MEG-only model. A separate backwards step-wise analysis with the neuropsychological scores as predictors was performed against the baseline model. In the final step, the impact upon model fit of adding the retained MEG predictor variables, to the neuropsychology model was assessed.

5.2 Results

5.2.1 Behavioural comparison of memory clinic patients with other groups

5.2.1.1 MEG congruency judgement task

Performance of the MEG congruency judgement task for the MC group was close to ceiling ($\bar{x}$=97.8%, SD=2.26% correct), like the control but not pAD group. Only correct trials were included in subsequent MEG analyses (whereas all trials were included for the pAD group).

5.2.1.2 Cued Recall

The MC group cued recall scores were comprised almost entirely from recall of congruent items, as only one of these patients correctly recalled an incongruent item. Total cued recall scores ($\bar{x}$=27.6%, SD=11.8% correct) were significantly lower for these patients compared with the control group (*t(44.2)=5.60, p<.001*) and far more variable (*Levene's F=13.2, p=.001*), as evident in *Figure 5.1a*. Cued recall was superior in the MC relative to pAD group (*t(33)=2.87, p=.007*). As is evident from *Figure 5.1a*, the MC group had a greater range of scores (though range of pAD scores may have been reduced by floor effects). Both groups had performed the preceding cued recall task.

Within the MC group, cued recall correlated significantly with not only the ACE-R memory sub-component (this accounted for 37.5% of variance in cued recall performance) but also with attention/orientation and visuo-spatial sub-components (49.8% and 17.5% of variance accounted for respectively) (*Memory: r(28)=.612, p=.001; Attention/Orientation: r(28)=.706, p<.001; Visuo-Spatial: r(28)=.418, p=.027*).

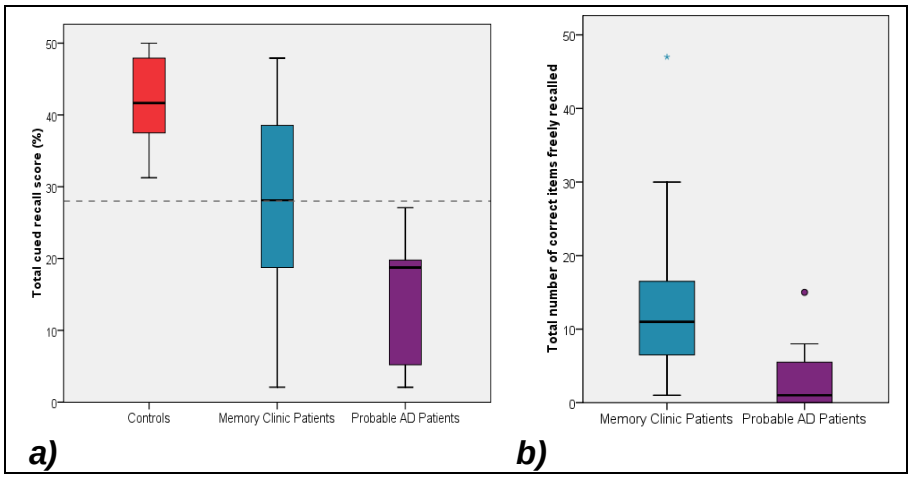


Figure 5.1: Recall for MEG task items

a) Cued recall score in control, MC and pAD groups. Reference line indicates cut-off threshold for 'normal' versus 'low' recall performance; b) Free recall scores in MC and pAD groups.

5.2.1.3 Free Recall

One patient was excluded from this measure as an outlier, correctly recalling 47 items (the highest score within the younger group in chapter 2 was 34 items). When questioned after testing, the patient described using a strategy whereby she would first select a general category (e.g. animals or places) and would then visualise moving through a space (e.g. west to east, high to low) recalling all the task items she encountered on her journey through that space. The remainder of the MC group did not demonstrate a floor effect and correctly recalled significantly more items than the pAD group

(*Z(37)=3.00,sig=.001*), see *Figure 5.1b*. Free recall scores within the MC group correlated with the memory sub-component of the ACE-R only, accounting for 35.5% of variance (*r(27)=.594, p=.001*).

5.2.1.4 Neuropsychological test scores

The MC group scored lower than the control group (who were almost entirely at ceiling for attention/orientation and visuo-spatial sub-components) for all measures except the language sub-component and was significantly more variable on all measures except for verbal fluency and language (*ACE-R: Total: t(44.9)=5.822, p<.001; Memory: Z(47)=4.13, sig<.001; Verbal Fluency: Z(47)=2.52, sig=.008; Language: Z(47)=0.537, sig>.29*). MC patients performed better than pAD patients for total ACE-R score and all sub-components, and were less variable for language, attention/orientation and visuo-spatial sub-component measures (*ACE-R: Total: t(36)=6.65, p<.001; Memory: Z(38)=3.54, sig<.001; Visuo-Spatial: Z(38)=2.39, sig=.011; Attention/Orientation: Z(38))=2.71, sig=.006; Verbal Fluency: Z(38)=2.70, sig=.003; Language: Z(38)=2.38, p=.010*). See *Figures 5.2a-f.*

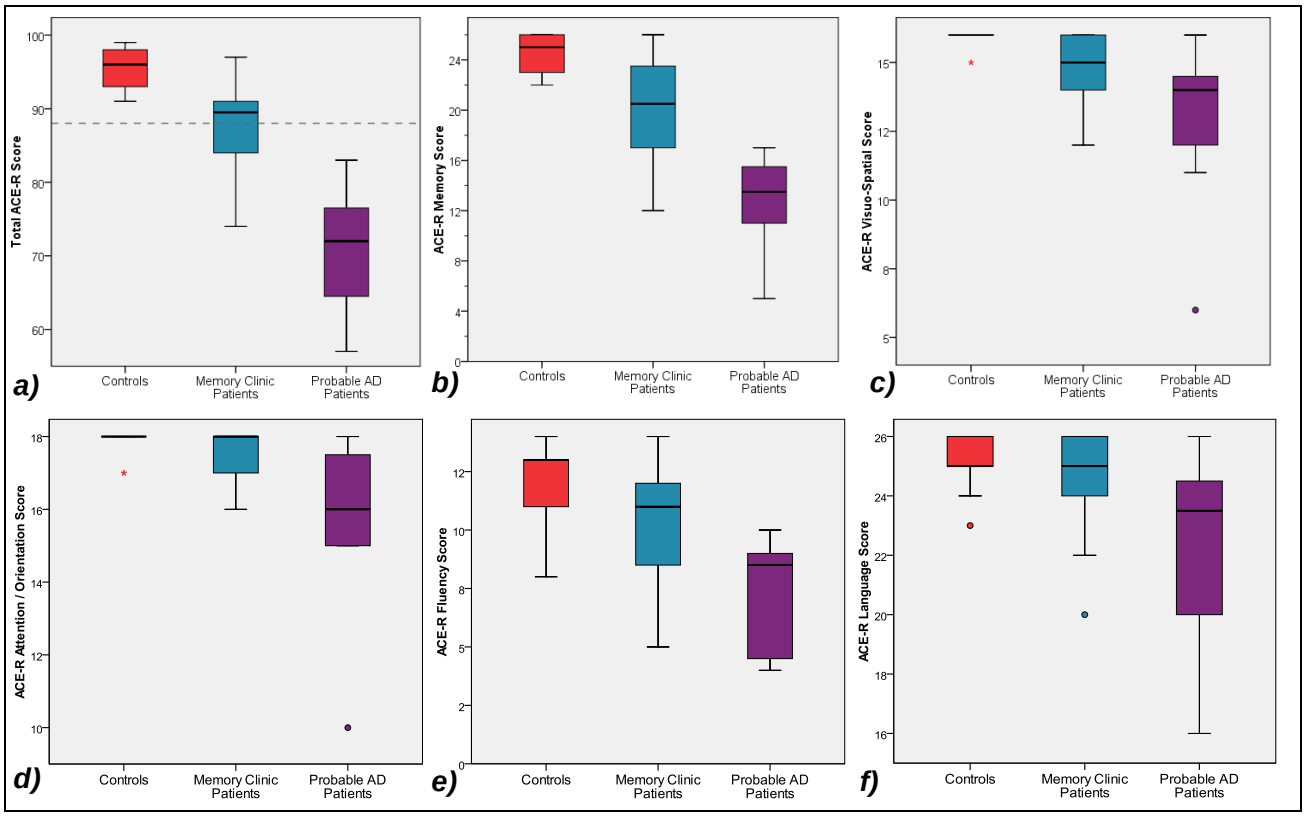


Figure 5.2: Behavioural measures in memory clinic patients and other groups
Box plots of ACE-R scores: a) Total ACE-R score, reference line indicates cut-off threshold of 88, at and above which prognosis is good; b) Memory component scores; c) Visuo-spatial scores; d) Attention / Orientation scores; e) Verbal fluency scores; f) Language scores.

Of the 30 MC patients, 16 scored above the cut-off threshold of 88 on the ACE-R battery, considered a 'good prognosis' (Mitchell, et al., 2009). Within the MCI sub-group, which comprised 8 individuals in total, 6 scored below this cut-off threshold (compared with 10 out of 22 in the WW sub-group).

5.2.2 SNR

It was necessary to exclude 2 MC patients from further analyses, due to SNR below 3 (ID 224: SNR=1.14 and 0.72; ID 278: SNR=1.18 and 2.13 for magnetometers and gradiometers respectively). This was due to inability to remove large widespread artefacts resulting from ferro-magnetic dental work.

SNR for the remaining 28 patients was high with means of 22.9 (14.1) and 28.1 (17.1) for magnetometers and gradiometers respectively. As seen for all other groups, gradiometers had higher SNR than magnetometers (*Magnetometers-Gradiometers: Z=-2.96, sig=.003*). SNR did not differ significantly between MC and control (*control-MC: Magnetometers: Z=-1.64, sig>.1; Gradiometers: Z=-0.754, sig>.4*) or pAD groups (*MC-pAD: Magnetometers: Z=-1.26, sig>.22; Gradiometers: Z=-0.723, sig>.48*).

5.2.3 MEG measures in MC group

5.2.3.1 N400m congruency effect

CE latency did not significantly differ between MC and other groups in either sensor type (control-*MC: MEG021m: t(54)=-0.730, p>.23; MEG161g: t(54)=-0.628, p>.26; MC-pAD: MEG021m: t(34)=0.629, p>.52; MEG161g: t(34)=-0.650, p=.26*). Comparison of MC group average topographies in *Figures 5.3d&e* with those of the other groups *(Figures3.3-4 & 4.4-5*) suggested lesser magnitude reduction than for the pAD group in relation to controls, a pattern evident at the majority of ROIs (*Figures 5.3a&b*), although a statistically significant difference occurred only at the right fronto-temporal magnetometer MEG122m between control and MC groups (*MEG122m: t(54)=2.12, p=.020; MEG144g: t(54)=1.56, p=.063*). Despite markedly greater CE magnitude on average at the left posterior temporal gradiometer MEG161g for MC relative to pAD patients, the measure was highly variable and the difference was not significant (*t(34)=1.13, p>.13*). The time course in *Figure 5.3c* implied that control – MC group differences were driven by increased N400m magnitude for congruent items, whilst the pattern of reduction of N400m for incongruent items seen in the pAD group was not evident in the MC group average.

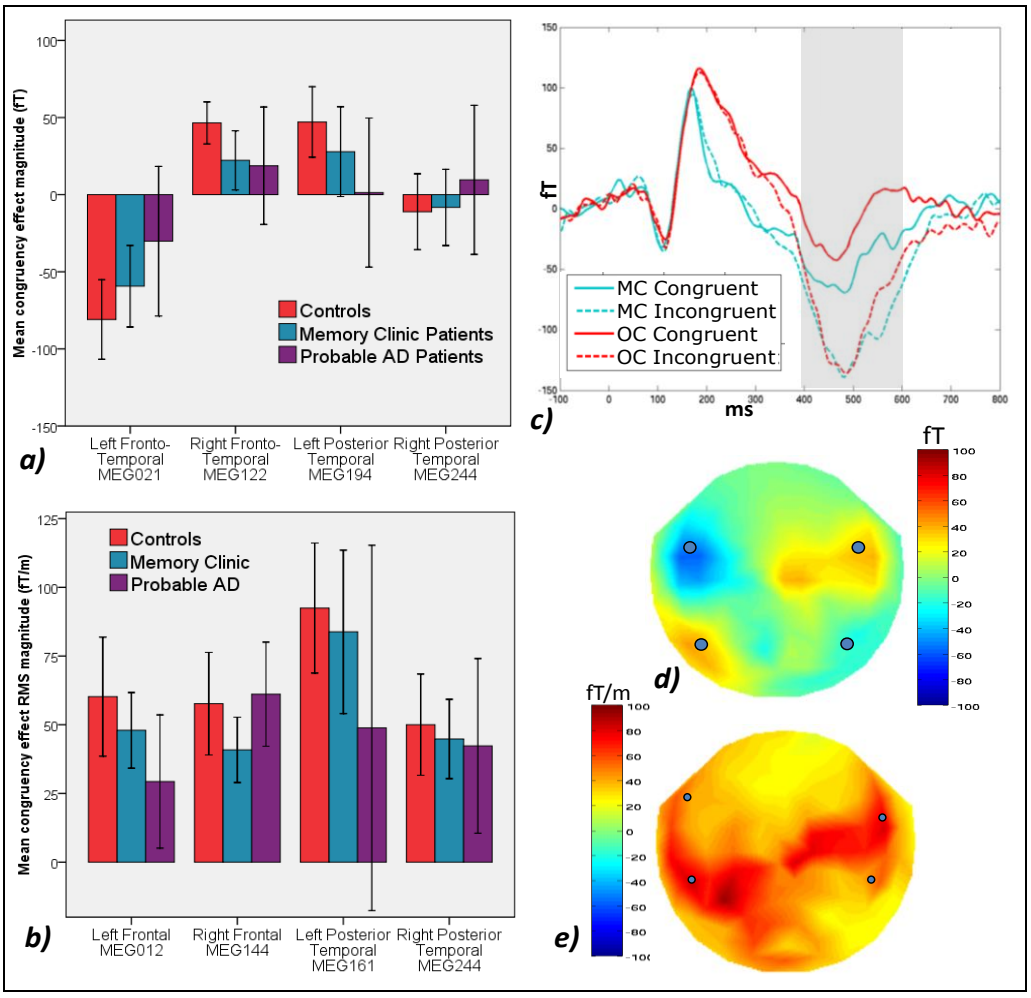


Figure 5.3: N400m Congruency Effect in MC group

a) & b) Mean CE magnitude at magnetometer and gradiometer ROIs respectively, for control, MC and pAD groups. Error bars indicate 95% confidence intervals; c) Group mean time courses of initial conditions at MEG021m in control and MC groups; d) & e) MC group mean CE topographies from 400-600ms in magnetometers & gradiometers respectively, ROI locations are indicated.

5.2.3.2 N400m incongruent repetition effect

There were no significant latency differences between MC and other groups at either the magnetometer or gradiometer ROI (control-*MC: MEG021m: t(54)=0.581, p>.56; MEG161g: t(54)=0.109, p>.91; MC-pAD: MEG021m: t(34)=0.643, p>.52; MEG161g: t(34)=1.48, p>.14*), nor were there significant differences in IRE magnitude at gradiometer ROIs (*Figure 5.4b*). The group average time course in *Figure 5.4c* illustrates the absence of an IRE in the MC group at right fronto-temporal magnetometer ROI MEG132m, where magnitude reduction relative to controls did reach significance (control-*MC: t(54)=2.57, p=.007*), *Figure 5.4a*. IRE magnitude was greater in the MC

relative to pAD group at left posterior temporal magnetometer ROI MEG164m (*MC-pAD: t(34)=1.89, p=.034*).

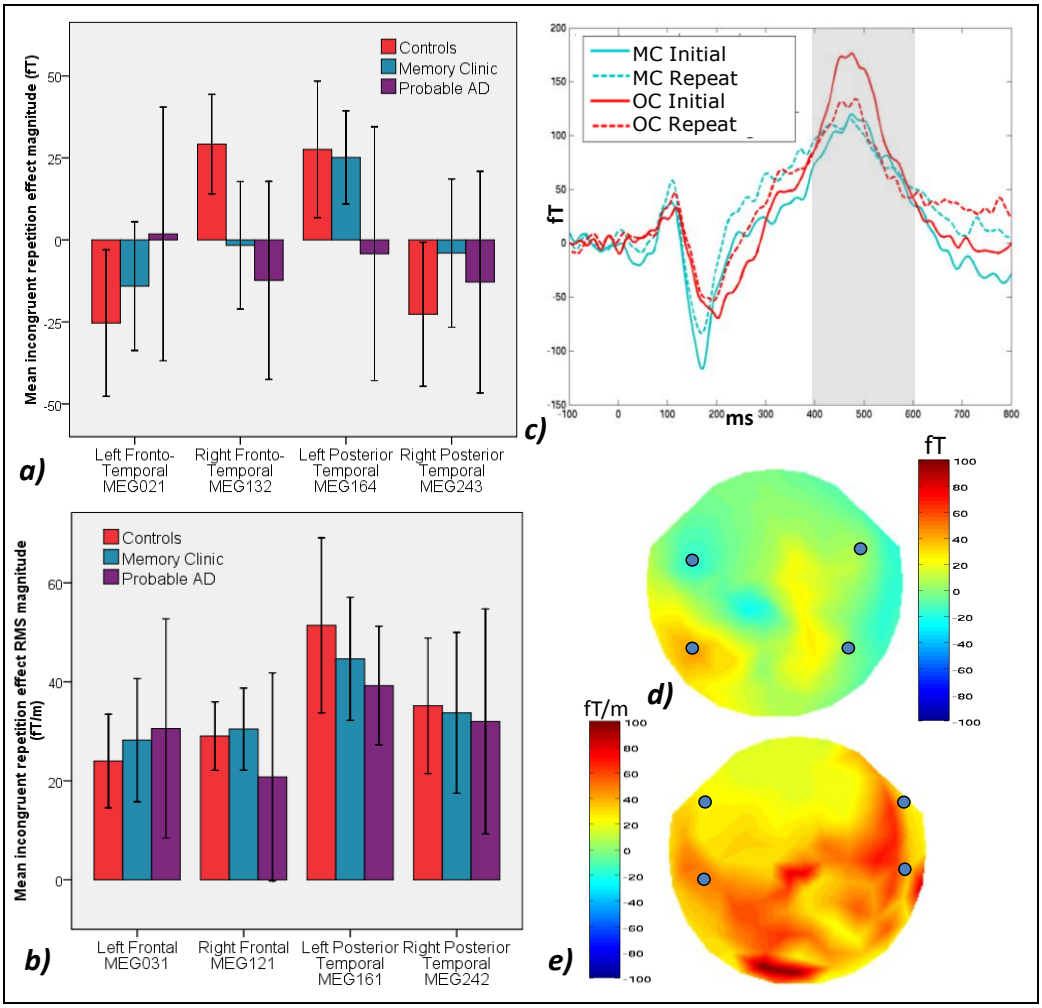


Figure 5.4: N400m incongruent repetition effect in MC group

a) & b) Mean IRE magnitude at magnetometer and gradiometer ROIs respectively. Error bars indicate 95% confidence intervals; c) MC and control group mean time courses of initial and repeat incongruent conditions at left fronto-temporal magnetometer MEG132m; d) & e) MC group mean IRE topographies across 400-600ms time window, for magnetometers and gradiometers RMS of difference respectively, ROI locations are indicated.

5.2.3.3 P600m congruent repetition effect

CRE FAL was significantly shorter, by a mean of 37.6ms (SE=17.6ms), for MC than pAD patients at magnetometer MEG173m, whilst FAL did not significantly differ at this ROI between MC and control groups (control-*MC: t(54)=1.79, p=.080; MC-pAD: t(33)=-2.13, p=.021*), see *Figures 5.5c-d.*

CRE magnitude within the MC group compared to controls showed a near-significant trend for reduction at the same ROI MEG173m (*control-MC: t(54)=-1.62, p=.056*), see *Figure 5.5a*, but a highly significant decrement at the left posterior temporal gradiometer MEG164g (*control-MC: t(45.4)=3.07, p=.002*), see *Figure 5.5b*. The pattern

of CRE magnitude enhancement relative to pAD patients and decrement relative to controls was evident in comparison of the group average topographies in *Figures 5.5e&f* with those in *Figures 3.9-10 & 4.8-9*. However, given high variability, only a near-significant reduction of CRE magnitude for pAD relative to MC patients occurred, at the left fronto-temporal magnetometer MEG021m (*MC-pAD: t(34)=1.58, p=.062*).

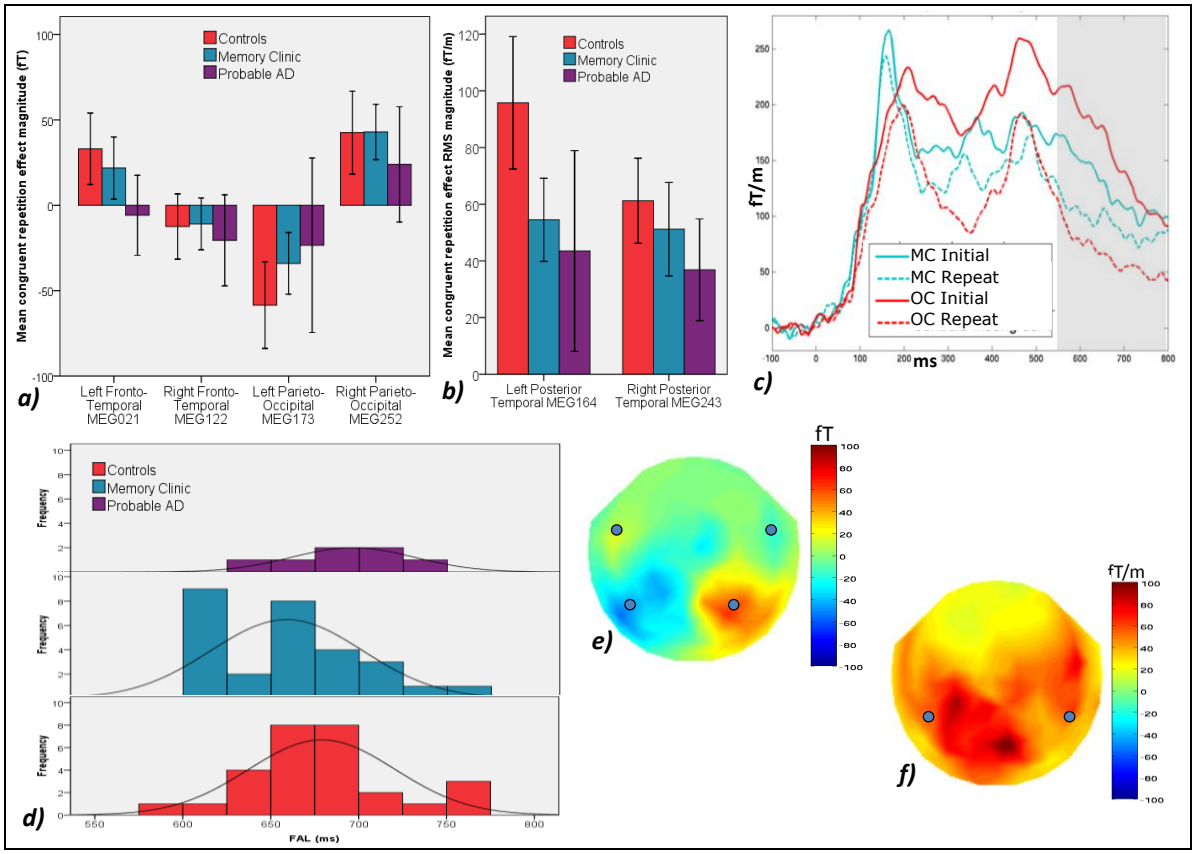


Figure 5.5: P600m Congruent Repetition Effect in memory clinic group

a) & b) Mean CRE magnitude in control, MC & pAD groups, at magnetometer and gradiometer ROIs respectively. Error bars indicate 95% confidence intervals; c) MC and control group mean RMS time courses of initial and repeat congruent conditions at left posterior temporal gradiometer MEG164g; d) FAL of CRE at left parieto-occipital magnetometer MEG173m; e) & f) Group mean topographies across 550-800ms time window, for magnetometers & gradiometers RMS of difference respectively, ROI locations are indicated.

5.2.3.4 Early repetition effect

A non-significant trend for FAL of the early repetition effect to be delayed in MC patients relative to controls, with a mean difference of 16.5ms (SE=10.7ms), occurred at left magnetometer ROI MEG151m (*t(54)=-1.54, p=.065*).

A pattern of significant RE magnitude reduction at *left* hemisphere gradiometer ROIs and the right magnetometer ROI was evident for the MC compared to control group (*control-MC: MEG241m: t(54)=-1.81, p=.038; MEG034g: t(43.7)=2.27, p=.014; MEG173g: t(48.4)=2.92, p=.003*). The pAD group demonstrated a significantly greater

RE magnitude decrement than the MC group at a *right* hemisphere gradiometer ROI and the left magnetometer ROI (*MC-pAD: MEG151m: t(34)=2.36, p=.012; MEG243g: t(34)=2.01, p=*.027), see *Figures 5.6a-e.*

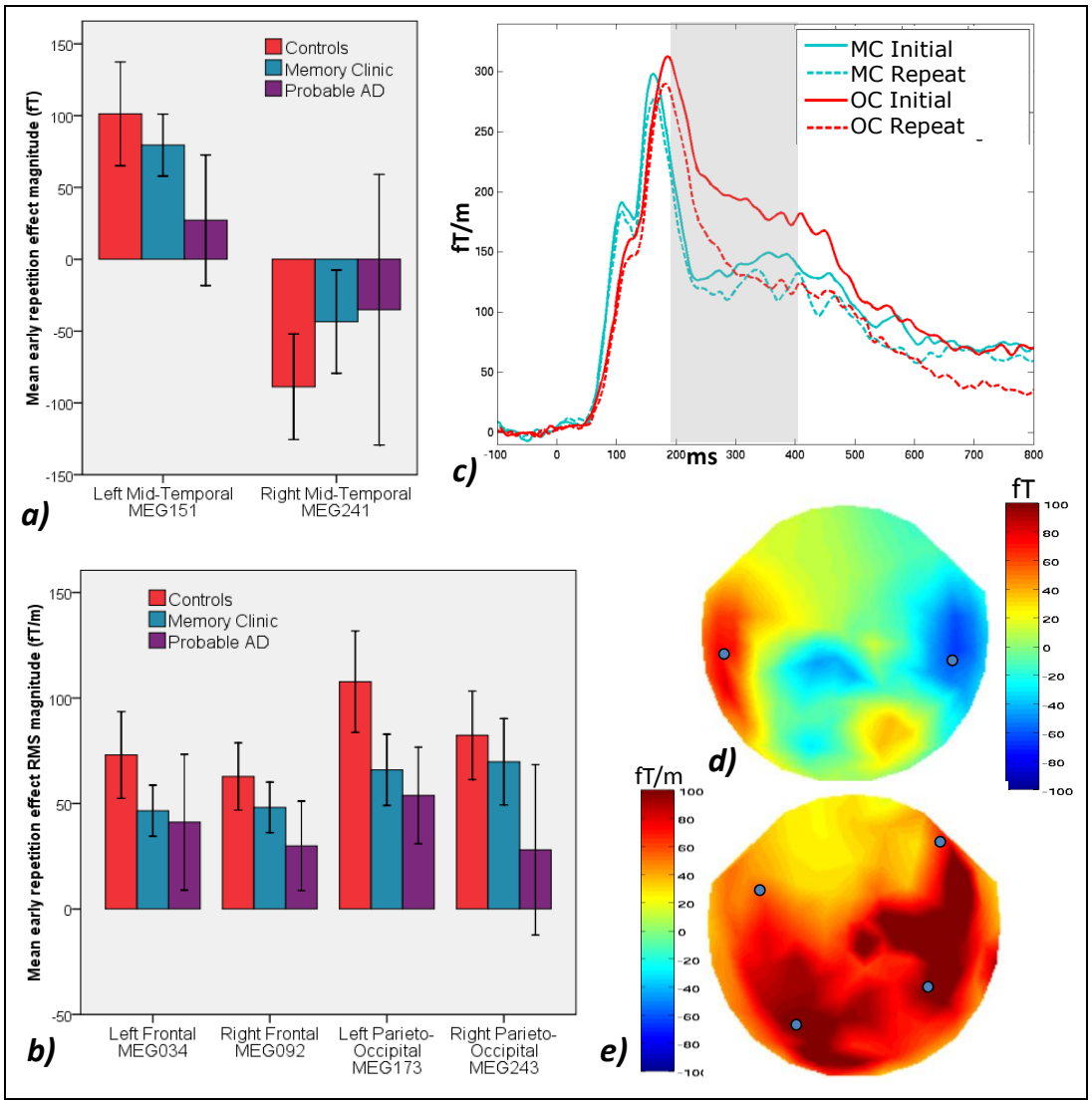


Figure 5.6: Early Repetition Effect in memory clinic patients

a) & b) Mean RE magnitude at magnetometer and gradiometer ROIs respectively. Error bars indicate 95% confidence intervals; c)Control and MC group mean RMS time courses of initial and repeat conditions at left parieto-occipital gradiometer MEG173g;
d) & e) MC group mean RE topographies from 200-400ms, for magnetometers and gradiometers RMS of difference respectively, ROI locations are indicated.

5.2.4 Relationships between MEG measures and behaviour

Correlations within the MC group of all behavioural measures with the MEG measures that significantly differed from other groups, and with MEG LR model and 10th percentile metrics, are listed in *Table 5.1*.

5.2.4.1 N400m congruency effect

CE magnitude at the right fronto-temporal magnetometer ROI CE122m correlated positively within the MC group with cued recall, ACE-R total score and multiple sub-components (attention/orientation, verbal fluency and language), though the relationship with the memory sub-component was not significant after correction for multiple comparisons. Scatterplots in *Figures 5.7 a-d* demonstrate one outlier, which did not, however, drive the correlations. Although tendencies were evident, there was no clear clustering of the MCI or WW sub-groups defined by the clinician. The relationships between CE magnitude and behaviour appeared to hold for the control group, but broke down within the pAD group.

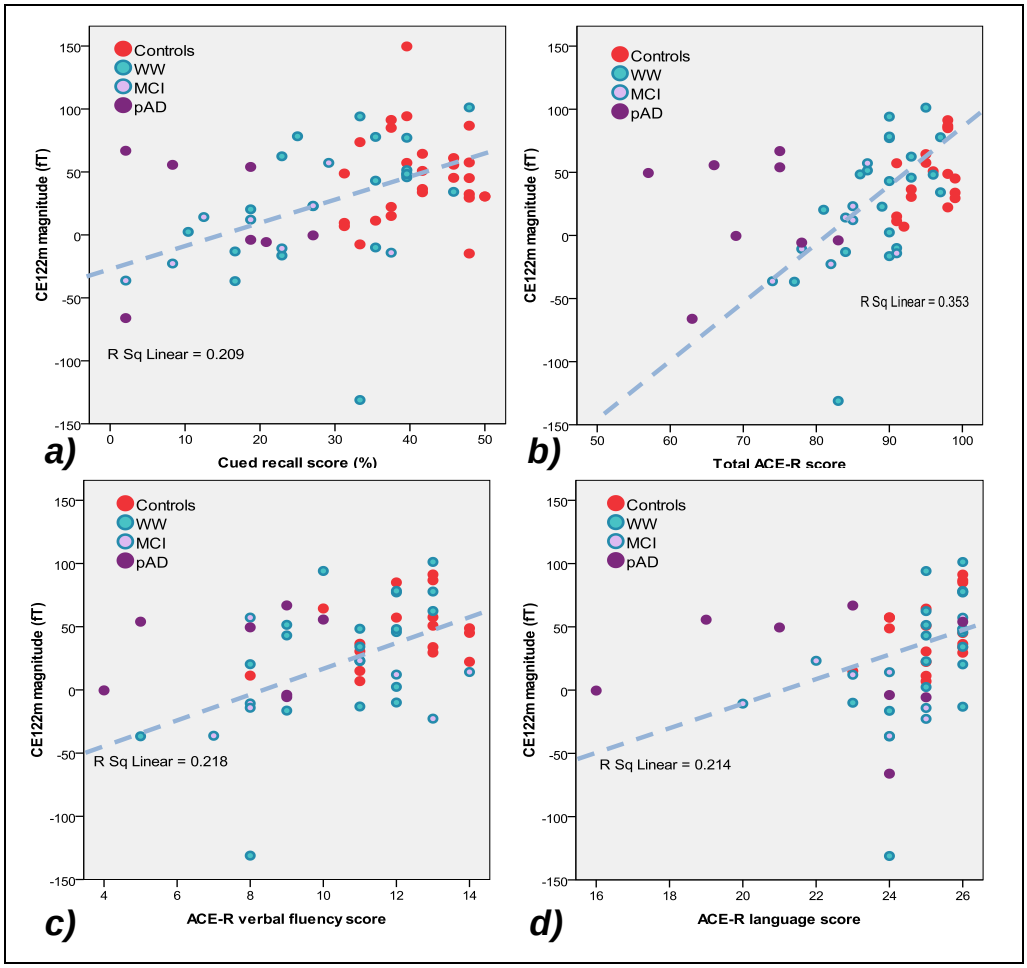


Figure 5.7: Relationships between N400m congruency effect and behavioural test scores
a)-d) Relationship of effect magnitude at CE122m with cued recall score, ACE-R total score, ACE-R verbal fluency and ACE-R language sub-components respectively.
Fit lines are for entire MC group only.

5.2.4.2 N400m incongruent repetition effect

The relationships of IRE magnitude at the right fronto-temporal magnetometer ROI IRE132m with behavioural measures were similar to those found for the CE, except that

correlation with the ACE-R attention/orientation sub-component was not significant after correction. *Figures 5.8a-d* illustrate that magnitude was more variable within both MC and control groups than for CE, with IRE magnitude bunched below zero for the MCI sub-group but rising above zero for around only half of the WW sub-group. Clustering along both dimensions into MCI/WW sub-groups was somewhat evident in all plots, except for that depicting the relationship with ACE-R verbal fluency.

Table 5.1: Correlations between MEG and behavioural measures in MC group

		Recall		ACE-R					
		Cued (N=28)	Free (N=27)	Total (N=28)	Memory (N=28)	Vis-Spat (N=28) #	Attention (N=28) #	Fluency (N=28)	Language (N=28)
CE122m *	r	.458	.121	.594	.351	.264	.479	.467	.463
	p	.007	.274	.000	.034	.087	.005	.006	.007
IRE132m *	r	.379	.247	.631	.330	.198	.341	.613	.435
	p	.023	.107	.000	.043	.156	.038	.000	.010
CRE164g **	r	.225	.236	.276	.291	-.150	.132	.085	.213
	p	.125	.118	.077	.066	.223	.252	.334	.139
FAL CRE173m **	r	-.252	-.293	-.127	-.147	-.165	-.071	.018	-.002
	p	.098	.069	.260	.228	.200	.360	.464	.495
RE173g (left) **	r	.302	.223	.237	.116	.207	-.025	.051	.377
	p	.059	.131	.112	.278	.146	.450	.399	.024
RE243g (right) **	r	.293	.268	.334	.427	-.094	.246	.114	.025
	p	.065	.088	.041	.012	.317	.104	.281	.450
MEG 10th percentile *	ρ	-.279	-.254	-.393	-.456	.157	-.185	.019	-.435
	p	.075	.101	.019	.007	.212	.173	.462	.010
MEG LR model *	r	-.323	-.492	-.383	-.532	.134	-.153	-.051	-.098
	p	.047	.005	.022	.002	.248	.219	.398	.310

Corrected alpha level for ROI/model: * = .025; ** = .0125.
Blue shading = correlation significant at corrected alpha level (one-tailed); grey shading = correlation significant at p=.05 level (one-tailed), uncorrected.
Spearman's correlation coefficient was used for comparisons involving the 10th percentile metric, ACE-R attention/orientation and visuo-spatial sub-components.

5.2.4.3 P600m congruent repetition effect

There was no significant relation of any behavioural measure with CRE magnitude at the left posterior temporal gradiometer ROI CRE164g, or with CRE FAL at the left parieto-occipital magnetometer MEG173m. The closest relationship was of CRE164g magnitude with the ACE-R memory sub-component, which is depicted in *Figure 5.9a*. Although there was a tendency for lower magnitudes in those classified as MCI relative to WW, no obvious clustering was evident according to these sub-groups.

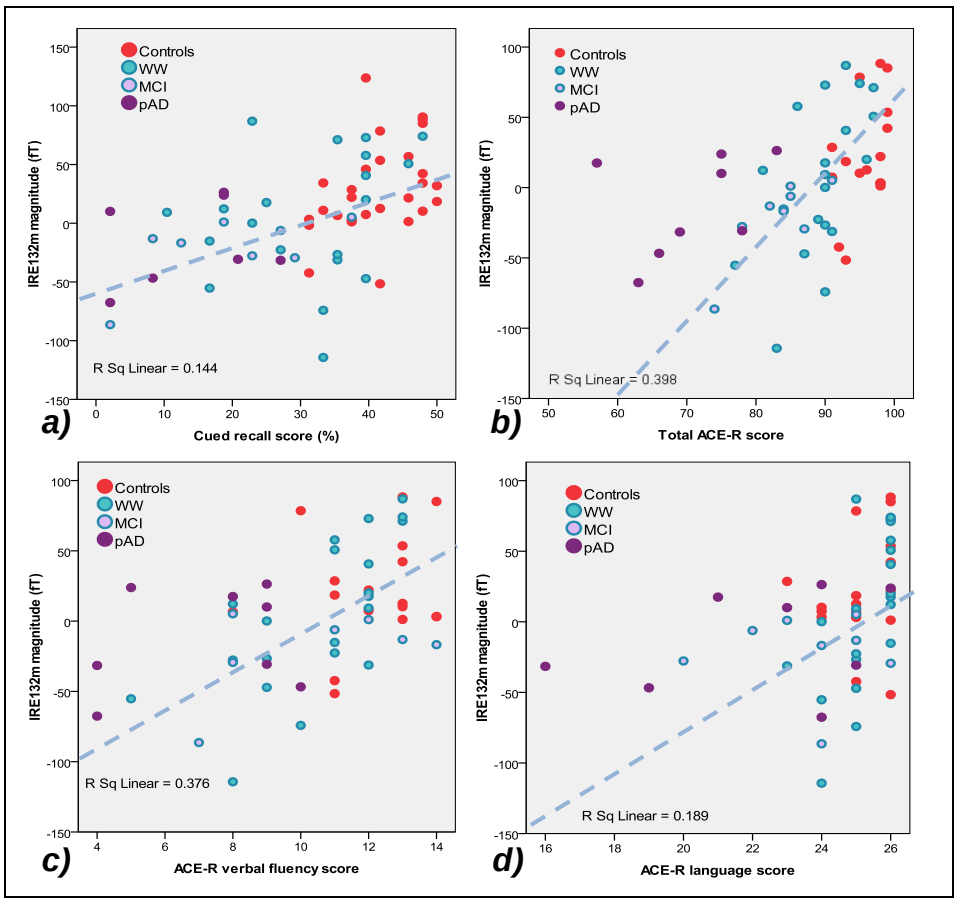


Figure 5.8: Relationship between N400m incongruent repetition effect and behavioural scores
a)-d) Relationship of IRE magnitude at IRE132m with cued recall score, ACE-R total score and ACE-R verbal fluency and language sub-components, respectively.
Fit lines are for entire MC group only.

5.2.4.4 Early repetition effect

RE magnitude at the right parieto-occipital gradiometer ROI RE243g, which differed between MC and pAD but not MC and control groups, showed strong positive correlation with the ACE-R memory sub-component. *Figure 5.9b* illustrates clustering of MCI-classified cases with low ACE-R memory score and low magnitude at this ROI. Both the MC/pAD group magnitude difference and the correlation with behaviour appeared to be driven by a subset of the WW-classified cases who performed well on the ACE-R

memory sub-component and had high magnitude RE at this ROI. A positive correlation between effect magnitude at the left posterior gradiometer ROI RE173g and ACE-R language score was not significant after Bonferroni correction. Despite a tendency for lower magnitude at RE173g in MCI-classified cases, as seen in *Figure 5.9c* there was no clear clustering according to MCI/WW sub-groups.

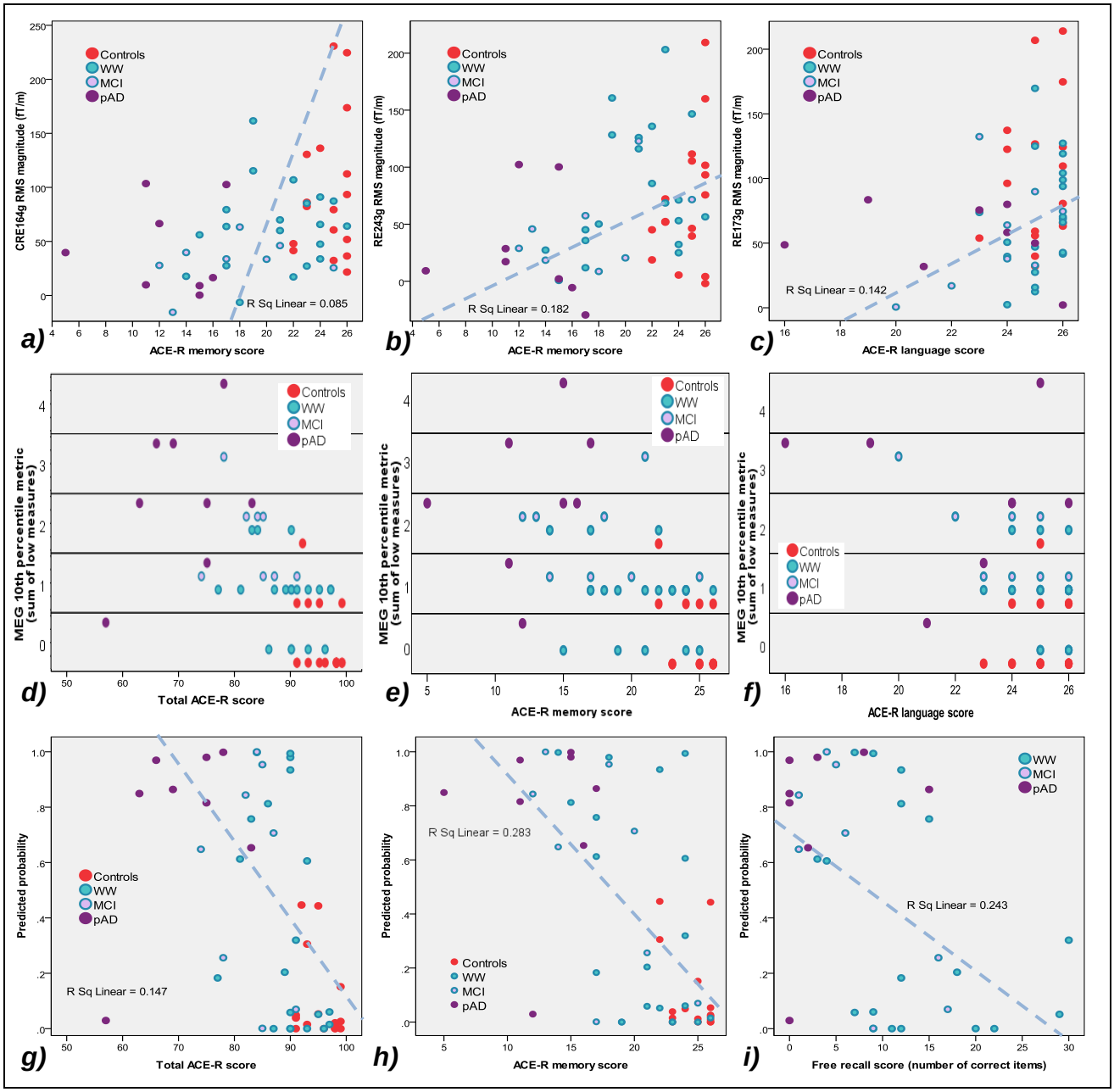


Figure 5.9: Relationships between behavioural tests and MEG measures: congruent and early repetition effects, 10th percentile metric and control/pAD LR model
a) CRE magnitude at CRE164g with ACE-R memory; b)-c) RE magnitude at right parieto-occipital gradiometer ROI RE243g with ACE-R memory score and left parieto-occipital gradiometer ROI RE173g with ACE-R language score; d)-f) MEG 10th percentile sum of low measures with total ACE-R, ACE-R memory and ACE-R language scores; g)-i) Probability of dementia according to LR model with total ACE-R, ACE-R memory and ACE-R language scores, respectively.
Fit lines are for entire MC group only.

5.2.4.5 MEG 10th percentile model

The MEG 10th percentile metric, which had only 5 levels (values of 0-4 effects of interest below the cut-off threshold), showed significant negative correlations with ACE-R total score and with memory and language sub-components. There was clear clustering of pAD cases when this metric was plotted against ACE-R total and memory scores, and MCI- and WW-classified cases were reasonably well-separated although there was some overlap, see *Figures 5.9d-e*. This was less evident for ACE-R language scores, see *Figure 5.9f*.

5.2.4.6 MEG LR model

Probability of dementia obtained via application of the LR model developed in the last chapter to the MC group data, correlated significantly with free recall, ACE-R total and ACE-R memory sub-component. As evident in *Figures 5.9g-i*, there was tendency for predicted probabilities to fall towards extremes (close to 1 or 0) and the MCI and WW cases classified by the clinician were not clearly separated by this MEG metric. Although the MCI cases who performed poorly upon free recall had high predicted probabilities and those who performed better had low probabilities of dementia according to the model (*Figure 5.9i*), this was less evident when considering the ACE-R memory score (*Figure 5.9h*) and this pattern was practically reversed when examining the relationship with ACE-R total for MCI cases alone (*Figure 5.9g)*.

5.2.5 Agreement of behavioural and MEG metrics with clinician's opinion

Of the 30 MC patients, the clinician identified 8 individuals whom he considered were highly likely to be suffering from incipient dementia, these comprised the MCI sub-group, whilst 22 individuals (73%) were classified as WW. Using the AUC for ROC curves, all 3 primary behavioural measures, total ACE-R score, cued recall and free recall were significantly better than chance at predicting which individuals were classified as MCI by the clinician, as was the MEG 10th percentile metric. Perhaps surprisingly the 10th percentile metric outperformed the LR model, which failed to perform significantly better than chance, see *Table 5*.2 and *Figure 5.10a*.

For the MEG measures, considering the ROI that differed most between MC and control groups for each effect of interest, the CRE was significantly better than chance, and comparable to the 10th percentile metric, at predicting the clinician's classification (see *Figure 5.10c*). *Table 5.2* quantifies sensitivity and specificity of each of these

measures to MCI-classification, along with the threshold selected that optimised discrimination between MCI- and WW-classified cases (as defined in section 5.1.3.3). Taking these threshold values, greatest sensitivity but least specificity were provided by cued recall, ACE-R total and CRE magnitude. Free recall, the ACE-R language sub-component and MEG 10th percentile metric had lower sensitivity but greater specificity.

Table 5.2: Significance of measures' ability to classify WW and MCI sub-groups

Measure	AUC (SE)	Sig.	Optimal MCI/WW threshold (Control threshold)	Sensitivity (using control cut-off)	Specificity (using control cut-off)
Cued Recall	.766 (.096)	.031	30.0% (31.3%)	87.5%	60.0%
Free Recall	.757 (.109)	.038	7 (-)	62.5%	89.5%
ACE-R total	.791 (.092)	.018	88 (91)	87.5%	70.0%
ACE-R Memory	.719 (.117)	.075	22 (22)	87.5%	54.5%
ACE-R Visuo-Spatial	.553 (.124)	.666	16 (15)	62.5%	54.5%
ACE-R Attention/Orientation	.703 (.117)	.098	18 (17)	62.5%	59.1%
ACE-R Verbal Fluency	.572 (.141)	.559	9 (10)	50.0%	91.8%
ACE-R Language	.784 (.101)	.021	25 (24)	62.5%	81.8%
Congruency Effect (MEG122m)	.431 (.115)	.576	28.7fT (5.5fT)	87.5% (50%)	60.0% (75%)
Incongruent Repetition Effect (MEG132m)	.675 (.100)	.154	3.1fT (-5.8fT)	87.5% (75%)	55.0% (60%)
Congruent Repetition Effect (MEG164g)	.750 (.091)	.042	46.8fT/m (25.7fT/m)	87.5% (25%)	70.0% (85%)
Early Repetition Effect (MEG092g)	.681 (.122)	.140	32.3fT/m (24.6fT/m)	62.5% (50%)	75.0% (80%)
MEG 10th percentile metric	.747 (.101)	.045	1 (1)	50.0%	85.0%
MEG LR model	.663 (.108)	.186	50% (50%)	62.5%	65%

Of the ACE-R sub-components, none had greater sensitivity to MCI classification than the ACE-R total score, although the language sub-component was significantly more accurate than chance (see *Figure 5.10b*).

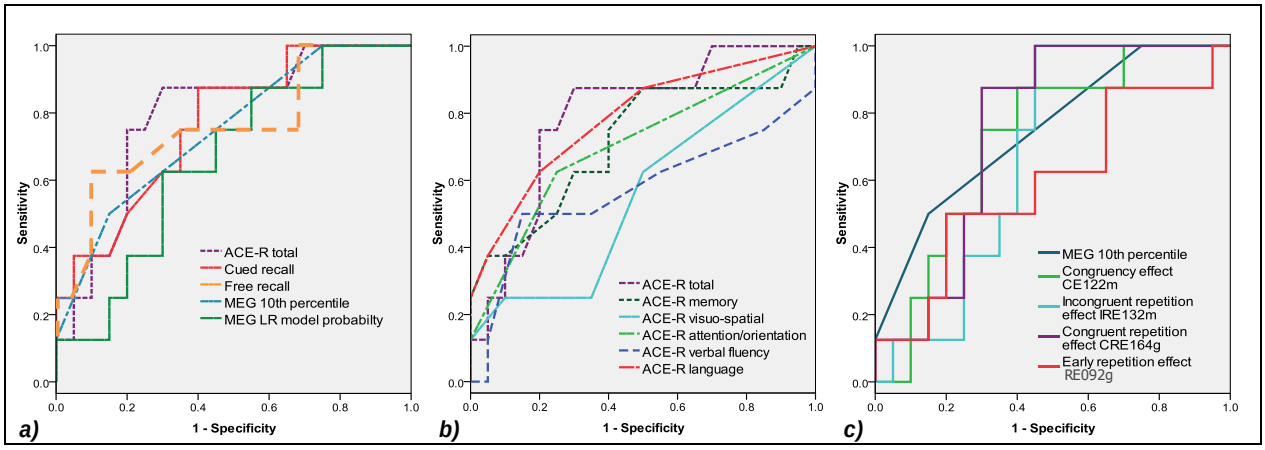


Figure 5.10: ROC curves of behavioural and MEG measures for clinician's MCI classification
a) Principal behavioural measures and MEG metrics; b) Neuropsychology (ACE-R);
c) MEG measures for each effect of interest and MEG 10th percentile metric

5.2.6 Logistic regression model for clinician's classification of MC patients

5.2.6.1 Neuropsychology-only MC group LR model

ACE-R total score was the only predictor variable retained when all sub-components and total score were subjected to the backwards step-wise procedure (*Table 5.3*). The resultant model (*-2LL=26.6, p=.009*) had an effect size of .312 and demonstrated 90% specificity but only 37.5% sensitivity to the clinician's classification of high likelihood MCI.

Table 5.3: Significant neuropsychological predictors for MCI classification

Predictor (Abbreviation)	Beta (SE)	Change in -2LL	Significance
ACE-R total (At)	-0.669 (0.300)	-6.88	.009
Constant	-2.86 (1.06)		.007

$\chi^2(1)=6.88$, $p=.009$, $R^2_N=.312$, overall accuracy = 76.7%

5.2.6.2 MEG-only MC group model

No IRE or RE predictor variables were retained in the MEG-only LR model. Of the CE predictor variables, right frontal gradiometer ROI CE144g, significantly improved the baseline model's ability to correctly classify MCI versus WW (*-2LL=28.7, p=.028*), with an effect size of .226. The accuracy of this CE model was equivalent to that of the neuropsychology-only model, with sensitivity and specificity of 37.5% and 90% respectively. Of the CRE ROIs, 2 were retained as predictor variables, left posterior temporal gradiometer ROI CRE164g significantly improved model fit (*-2LL=8.09, p=.004*), whilst left fronto-temporal magnetometer ROI CRE021m demonstrated a near-

significant trend (*-2LL=3.17, p=.075*). The resultant CRE model significantly improved discrimination between groups relative to the baseline model (*-2LL=25.3, p=.016*), with an effect size of .365. Accuracy was lower than that observed for either the model based upon ACE-R total score, or CE magnitude, with equivalent sensitivity of 37.5% but lower specificity at 80%.

When these retained predictor variables were combined in a backwards step-wise logistic regression procedure, the CE predictor variable was rejected, therefore the resultant MC group model was identical to that based upon the CRE only (*Table 5.4*).

Table 5.4: Significant MEG predictors for MCI classification, based upon individual effects of interest

Effect of interest modelled	Predictor	Beta (SE)	Change in -2LL	Sig.
Congruency Effect	Right frontal gradiometer CE144g	-1.86 (0.999)	-4.80	.028
	Constant	-1.84 (0.766)	-6.08	.014
Congruent Repetition Effect	Left fronto-temporal magnetometer CRE021m	1.23 (0.759)	-3.17	.075
	Left parieto-occipital gradiometer CRE164g	-3.36 (1.588)	-8.09	.004
	Constant	-3.51 (1.456)		.016

5.2.6.3 Neuropsychology and MEG combined MC group LR model

Addition of MEG predictor variables CRE164g and CRE021m, via a backward step-wise procedure, to the neuropsychology-only model resulted in retention of only the left gradiometer ROI CRE164g. The addition of this MEG predictor variable improved accuracy compared to the neuropsychology-only model with near-significance (*-2LL=3.79, p=*.052). Although specificity remained at 90%, sensitivity increased from 37.5% to 50%.

This full MC group model distinguished groups significantly more accurately than the baseline MC group model (*-2LL=22.8, p=.005*) with an effect size of .454 and satisfactory goodness-of-fit ($\chi^2(7)=9.84$, $p>.19$). Probability of MCI increased as each predictor decreased. Although ACE-R total score was a more significant predictor, the

greater beta value for the MEG predictor variable (as both predictors were based upon standardised z-scores) demonstrated greater predictive influence upon MCI classification (*Table 5.5*). There was no evidence for multicollinearity with tolerance at 0.924 and variance inflation factor (VIF) at 1.083.

All individuals had Cook's values of less than one (signifying no undue influence over the model outcome) and there were no outlying cases, with all standardised residuals below 2. As the classification plot in *Figure 5.11* illustrates, half of the WW cases had predicted probability of MCI below 25% and all had below 65% probability, whilst the MCI cases ranged in probability between 19.9-87.3%, indicating that the model had greater ability to exclude WW cases than to positively identify those classified as MCI.

Table 5.5: Predictors of MCI classification in combined neuropsychology and MEG model

Predictor	Beta (SE)	Change in -2LL	Significance
ACE-R total (At)	-0.698 (0.346)	-5.61	.018
Congruent Repetition Effect (CRE164g)	-2.10 (1.29)	-3.79	.052
Constant	-4.86 (2.01)		.016

**Model $\chi^2(2)=10.7$, $p=.005$; $R^2_N=.454$; Overall accuracy=78.6%*

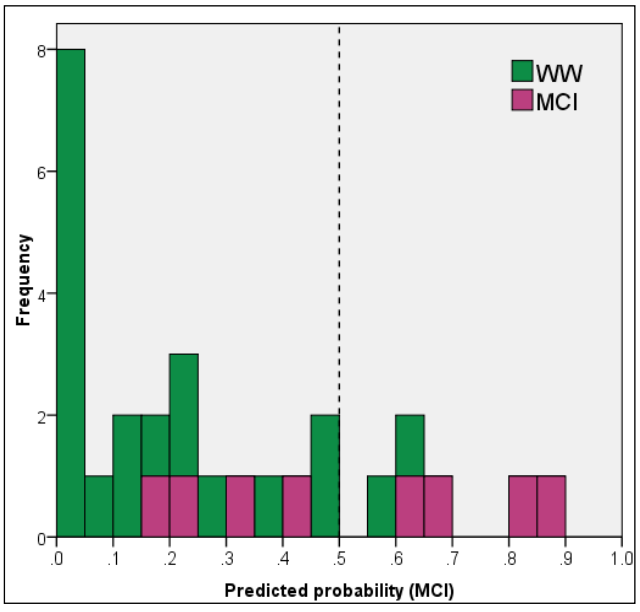


Figure 5.11: LR combined model's predicted probabilities of MCI within MC group

5.3 Chapter summary

This chapter sought to validate the application of the active MEG paradigm to a memory clinic (MC) group consisting of individuals classified by a clinician as either having mild cognitive impairment (MCI) or as "worried well" (WW). Spatio-temporal ROIs for effects of interest were defined from independent data on older controls versus pAD patients in the previous chapter and used to identify basic differences between the MC and other groups (Aim 1). Correlations of these MEG effects with behavioural measures were then reported (Aim 2). Most importantly, we went on to use ROC and logistic regression analyses to test the ability of 2 MEG metrics defined in chapter 4 (a logistic regression model and a 10^{th} percentile metric) to distinguish MCI and WW sub-groups; and in particular, the classification ability of these MEG metrics relative to the behavioural recall and ACE-R metrics (Aim 3). Findings are summarised below.

5.3.1 Behavioural measures

MC patients' performance was superior for all behavioural tasks in comparison with the pAD group. As a group, MC patients performed cued recall more poorly than the controls. For the ACE-R, MC patients' performance was lower than controls, but far more variable. The MC and control groups were both able to perform the MEG congruency judgement task close to perfectly, unlike the pAD group.

5.3.2 MEG findings in MC group (Aim 1)

5.3.2.1 N400m congruency effect

A general pattern of reduced CE magnitude for MC patients relative to controls reached significance only at a single magnetometer ROI, CE122m, which appeared to be driven by a larger N400m component for congruent items in the MC group. The lesser reduction in CE magnitude relative to controls that was apparent in MC compared to pAD groups did not reach significance at any ROI. Groups did not differ in CE latency.

5.3.2.2 N400m incongruent repetition effect

Magnitude of the IRE was reduced in MC patients relative to controls at the right fronto-temporal magnetometer ROI IRE132m, whilst it was reduced in the pAD relative to MC group at the left posterior temporal magnetometer ROI IRE164m. The MC group did not differ from the others on measures of latency, nor of magnitude in gradiometers.

5.3.2.3 P600m congruent repetition effect

CRE magnitude was significantly decremented in MC patients relative to controls at the left posterior temporal gradiometer ROI CRE164g. A pattern of non-significant reduced average CRE magnitude in MC patients relative to controls and in pAD relative to MC patients was apparent at several ROIs. This was the case at left parieto-occipital magnetometer ROI CRE173m, where FAL was significantly shorter for the MC than pAD group.

5.3.2.4 Early repetition effect

No significant RE latency differences were evident between MC and other groups. There was a pattern of significant RE magnitude reduction in left hemisphere gradiometer ROIs, and the right magnetometer ROI for the MC compared to control group, whereas the pAD group demonstrated diminution of the RE relative to MC group at opposite hemisphere ROIs.

5.3.3 Correlations between MEG measures and behaviour (Aim 2)

Magnitudes of both N400m effects correlated positively with cued recall, total ACE-R score and verbal fluency/language sub-components, whilst the CRE bore no significant relation to any behavioural measures. The RE at right gradiometer ROI RE242g correlated with the ACE-R memory component, with some evident clustering according to clinician's opinion, whereas reduced RE magnitude at left gradiometer ROI RE173g related to poorer language performance (although this did not survive correction for multiple comparisons) and there was no clear clustering of WW versus MCI cases. Number of abnormal measures according to the 10^{th} percentile metric correlated with ACE-R total score and memory and language sub-components and revealed some clustering of MCI/WW classified cases. Whilst predicted probability of dementia according to the LR model correlated with free recall and ACE-R total and memory scores, there was no clear clustering according to sub-group classifications.

5.3.4 Ability to predict MCI classification (Aim 3)

Of the behavioural measures, ACE-R total, cued recall and free recall performance were able to predict MCI/WW classification significantly above chance. Of the MEG measures, CRE magnitude and the 10^{th} percentile metric, but not pAD/control LR model, were able to predict MCI sub-group membership. Addition of the CRE predictor variable

improved the accuracy of the neuropsychology-only MC group LR model (an increase in sensitivity from 37.5% to 50%) with near-significance. This model's strength resided in its negative predictive power – i.e. the ability to correctly classify WW cases.

Chapter 6
Passive spoken word paradigm in healthy young individuals

In the following chapters we switch to a passive paradigm and examine more focal early, automatic responses associated with both acoustic perception and linguistic processes. The absence of a requirement to attend or respond to stimuli is particularly appealing in the context of patient studies, where task-comprehension and focus may comprise difficulties. Using spoken word/word-like stimuli, we examined modification according to linguistic parameters of the difference in the 'obligatory' auditory P50m response for infrequent minus frequent stimuli ('M50d') and the magnetic mismatch negativity (MMNm). M50d and MMNm are believed to reflect sensory gating and sensory/lexical memory respectively (see Chapter 1).

The modified version of a spoken-word MMN paradigm employed in the following chapters made use of acoustically highly similar standard 'stem' contexts comprised of either unintelligible noise, a pseudoword ('*kway*') or an actual English word ('*tray*' or '*play*'), with deviant stimuli constituted by addition of a final plosive (/d/ or /t/) to a stem, making a new word, pseudoword or noise stimulus. We adapted the stimulus sequence such that deviants occurred regularly after every fifth stem, with a minimum of 5 seconds and an average of 10 seconds between presentations of the same deviant; notably the identity of the deviant was unpredictable in line with more conventional MMN designs. Although deviant occurrence at regular positions in a repeating pattern fails to produce a MMN when attention is focused upon this pattern, in the absence of attention to such a pattern the MMN response is preserved (Sussman, 2007; Sussman, Winkler, Huotilainen, Ritter, & Naatanen, 2002). This adaptation of the standard MMN/odd-ball paradigm permitted us to examine in the same experiment the P50m auditory difference response enhancement for infrequent (deviant) stimuli relative to frequent (standard) stimuli (Boutros, et al., 1995). The longer minimum inter-stimulus interval (ISI) between deviant stimuli aimed to minimise inhibition resulting from a recent identical acoustic input. Previous work systematically varying ISI in an oddball paradigm found maximal P50 difference responses at a mean ISI of 10s for deviant stimuli (Ermutlu, et al., 2007), identical to that used here.

Our effects of interest corresponded to different levels of neural processing of incoming auditory speech signals as follows:

1. *'Sensory gating'* – Main M50d response: the contrast of the P50m to deviant stimuli minus the equivalent time window of the response to standard stimuli, reflecting ability to gate auditory stimuli according to their current relevance.

2. *'Sensory memory'* – Main MMNm response, reflecting change detection mechanisms and dependent upon sensory memory function.

3. *'Phonological processes'* – Contrast of M50d and MMNm responses to /d/ versus /t/ plosives, hypothesised to reflect ease of discrimination of word-final plosive endings.
Discrimination of */d/* plosive endings may be more difficult than for */t/* endings within the context of stimuli used here, in both purely acoustic and phonological terms. Reduced phonological salience of consistently-voiced plosives make these more difficult to detect than cases where voicing of penultimate phoneme and final plosive are inconsistent (Bird, Lambon Ralph, Seidenberg, McClelland, & Patterson, 2003). In our stimulus set, the voiced */d/* plosive was always consistent with the voiced stem and, additionally, had a shorter closure period between stem-offset and plosive-onset (typical of English phonology), whilst the unvoiced */t/* was always inconsistent and had a longer closure period, making */d/* plosives less salient in phonological as well as acoustic terms.

4. *'Lexical/Semantic processes'* – Contrast of M50d and MMNm responses to words versus nonwords, a potential index of neuronal memory traces for words.
Within the current paradigm, difference response features specific to word contexts may constitute neurophysiological correlates of lexical/semantic memory for content words. In the absence of attention to the stimuli, MMNm magnitudes for words have been found to be greater than that for phonologically similar pseudowords, for which there is no extant neuronal lexical representation (Shtyrov & Pulvermuller, 2002). Spoken pseudoword MMNm magnitude has been shown to be modulated by attention, whilst spoken word MMNm appears attention-independent (Garagnani, Shtyrov, & Pulvermuller, 2009). These findings have been interpreted as evidence that discrete neuronal representations, or memory traces, of words are obligatorily 'ignited' whenever they are encountered (Shtyrov, Kujala, & Pulvermuller, 2010).

5. *'Morpho-syntactic processes'* – Interaction during M50d and MMNm responses of plosive type and 'past' versus 'nonpast' stem contexts, indicative of automatic grammatical/morpho-syntactic processing.

With reference to the stimuli employed here, according to context, a */d/* plosive constitutes either a past-tense grammatical suffix (as in '*played*'; */d/* in a 'past' context) or its non-grammatical morphological twin ('*trade*'; */d/* in a 'nonpast' context), whereas adding a */t/* plosive to the same word stems produces '*plate*' and '*trait*'. These latter are morphological twins where */t/* serves no grammatical function. This dissociation allows us to disentangle the phonological and acoustic processing of the */d/* plosive. Several theories address the question of how inflected words are processed and understood. Dual mechanism accounts postulate separate contributions of a 'parsing' mechanism that strips a potential suffix (in English regular past tense this is always '-ed') and a lexical store. Some hypothesise that parsing occurs obligatorily for all potentially suffixed words (Marslen-Wilson & Tyler, 2007), whilst others believe that parsing is undertaken only upon those words for which there is not a full-form representation in the lexicon (Pinker & Ullman, 2002). The single mechanism connectionist account posits a distributed parallel process that draws upon both semantic and phonological knowledge (McClelland & Patterson, 2002; Woollams, Joanisse, & Patterson, 2009).

Aims & Predictions

In this chapter we characterised spatio-temporal features of evoked M50d and MMNm difference responses in a group of healthy young adults. Our specific aims were as follows.

Aim 1. Spatio-temporal localisation of M50d and MMNm

We aimed to identify spatio-temporal distributions of the main M50d and MMNm responses for each plosive type via the mass univariate sensor SPM approach. Spatio-temporal ROIs were selected from statistical maxima to avoid bias away from more anterior sensors that could arise if only considering magnitudes from group topographies (due to non-linear scaling of the signal with distance from its source). These ROIs were subsequently used to conduct factorised comparisons of the experimental conditions.

Aim 2. Characterise latency and magnitude according to linguistic variables

3-factor (stem x plosive x ROI) ANOVAs were used to identify sources of variance in latency or magnitude of M50d or MMNm between conditions. Unlike the active

paradigm, FAL was examined at each ROI (rather than just the maximal one): latency differences might be evident at ROIs other than where magnitude differences between conditions are maximal, and we wanted to maximise sensitivity to subtle delays in processing that might emerge particularly with regard to morpho-syntactic processes.

As the stem+plosive condition was always super-imposed onto ongoing stem-processing, the result of subtracting stem-only from stem+plosive conditions difference was primarily of positive magnitude. For consistency with the method employed in analyses of the active paradigm, we computed gradiometer magnitudes using the RMS of the difference response (see chapter 1). Our predictions were:

Phonological/acoustic processes: We expected reduced phonological/acoustic salience of */d/* relative to */t/* plosive-endings in the current stimulus set to be reflected in less prominent neuromagnetic responses.

Lexical/semantic processes: We hypothesised MMNm responses to be most prominent for conditions within word contexts. As no lexical effects have been reported for the P50(m), such effects were not explicitly anticipated to emerge in the current dataset.

Morpho-syntactic processes: Latency or magnitude differences for */d/* relative to */t/* endings might vary according to whether or not morphological decomposition is triggered. For example, given the assumption that only words for which there is no pre-existing lexical entry are decomposed, we might expect '*played*' but not '*trade*' to be processed in this way, with an associated delay for '*played*' relative to '*plate*' but not '*trade*' relative to '*trait*'. Alternatively, if all potentially suffixed words undergo morphological decomposition, or if lexical search and decomposition are parallel aspects of a single mechanism, latencies of '*trade*' and '*played*' would not be expected to differ.

Aim 3. Describe topographic properties according to linguistic variables

In terms of magnitude, effects of ROI in the above ANOVAs offered some indication of where effects were maximal in sensor space. Interactions of ROI with the effects of interest would demonstrate differential topography of processing according to condition demands. As noted previously (chapter 3) effects of ROI are difficult to attribute to specific hemispheric or rostrality differences in magnetometers, as the location of the signal is displaced from its dipolar source (chapter 1). Nonetheless, interaction of ROI with other factors in magnetometers would be indicative of topographic differences, albeit non-specific as to the cortical origin of these differences. Information about

laterality from gradiometer data, however, does constitute statistical evidence with regard to underlying sources, as the signal is maximal above underlying cortical generators (chapter 1). A normalised measure of laterality – the laterality quotient (LQ) – was used to remove confounds of different overall response magnitudes, which may influence interactions with hemisphere (or rostrality).

We expected relatively greater left-lateralisation for words relative to pseudowords, in keeping with previous findings (Pulvermuller, et al., 2001; Shtyrov, et al., 2010; Shtyrov, et al., 2005). Similarly, a left-sided emphasis was anticipated for conditions where syntactic processing (i.e. morphological decomposition) occurred (e.g. '*played*'), reflecting neurophysiological correlates of regular past-tense grammatical processing. The */d/* plosive in the pseudoword case ('*kwade*') *might* be processed as a regular past tense suffix, in keeping with some of the psycholinguistic theories noted above; we had no strong predictions as there is no extant lexical memory trace for this stimulus's stem.

6.1 Method

6.1.1 Participants

Eighteen native English speakers with a mean age of 25 years (SD=4.1 years), who reported no neurological or psychiatric history, were recruited from the MRC Cognition & Brain Sciences Unit volunteer panel. All participants were right-handed (tested according to Oldfield, 1971), gave written informed consent and were paid for their participation.

6.1.2 Design

A modified passive linguistic oddball paradigm was presented to participants in an MEG setting, whilst they watched a silent film. Four standard '*stem*' stimuli (2 English words, 1 pseudoword and 1 unintelligible average of the other 3 stems) were presented to the participant in separate blocks and comprised 80% of trials. Every fifth stimulus differed by pseudo-random addition of a */d/-* or */t/*-ending (equiprobably), producing different words and nonwords. See *Figure 6.1*.

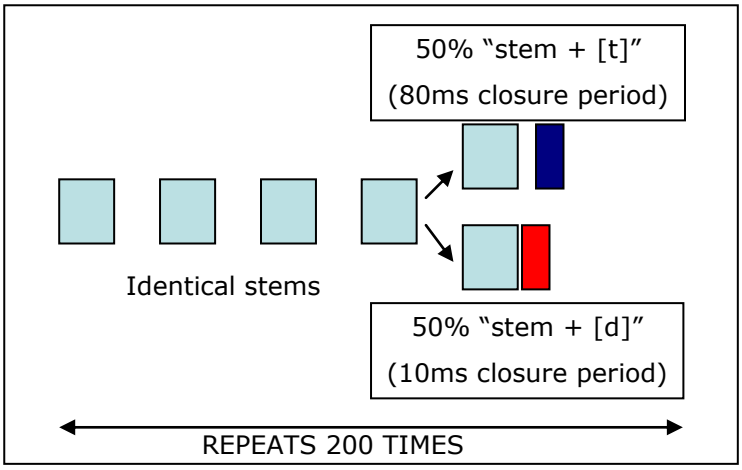


Figure 6.1: Trial sequence design
A different identical stem was used for each of 4 blocks; every fifth stem was followed, with equal probability, by either a [d] or [t] plosive ending

6.1.3 Stimuli

6.1.3.1 Features and construction

Stimuli were constructed from exemplars spoken by a female native British English speaker using Cool Edit 2000 (Syntrillium Software Corporation, Scottsdale, Arizona). All stems were 310ms in duration and matched for mean RMS power, fundamental frequency (F_0) and vowel duration. The 4 stems comprised the English words '*play*' and '*tray*', a phonetically similar pseudoword '*kway*' and an ambiguous 'noise' condition which was constructed from an average across acoustic spectra of the other 3 stems. The */d/* and */t/* endings were taken from recordings of the words '*hade*' and '*hate*', in order to avoid any potential co-articulation cues, and were identical for every stem context. These plosives were spliced onto the end of the stems to form the infrequent stimuli, with a closure period of 10ms and 90ms for */d/* and */t/* respectively. In accordance with the English phonology, the */d/* and */t/* plosives had mean RMS amplitude of -29.58dB (maximum -27.72dB) and -21.25dB (maximum -19.56dB) respectively, over their 77ms durations. See *Figure 6.2* for example stimulus waveforms.

6.1.3.2 Validation

To ascertain that we replicated the natural English phonology as closely as possible, these stem and closure durations were selected via behavioural pre-testing of a cohort of 20 token combinations for each word context (stem durations 290ms-320ms; closure periods 5-20ms for */d/* and 80-95ms for */t/*). Naturally spoken tokens ('*played*', '*plate*', '*trade*', '*trait*') were additionally included in the cohort.

Eighteen participants, who did not participate in the MEG experiment, were asked to listen to these tokens in a random order via headphones, to identify each word and rate how 'natural' it sounded it on a scale of 1-5 (1= 'not at all', 5='natural'). The spliced combinations rated as most natural were selected for inclusion as our experimental stimuli, of these, both '*played*' and '*trade*' were identified as such by 100% of participants, whilst 'plate' and 'trait' were identified as such by 16 out of 18 participants.

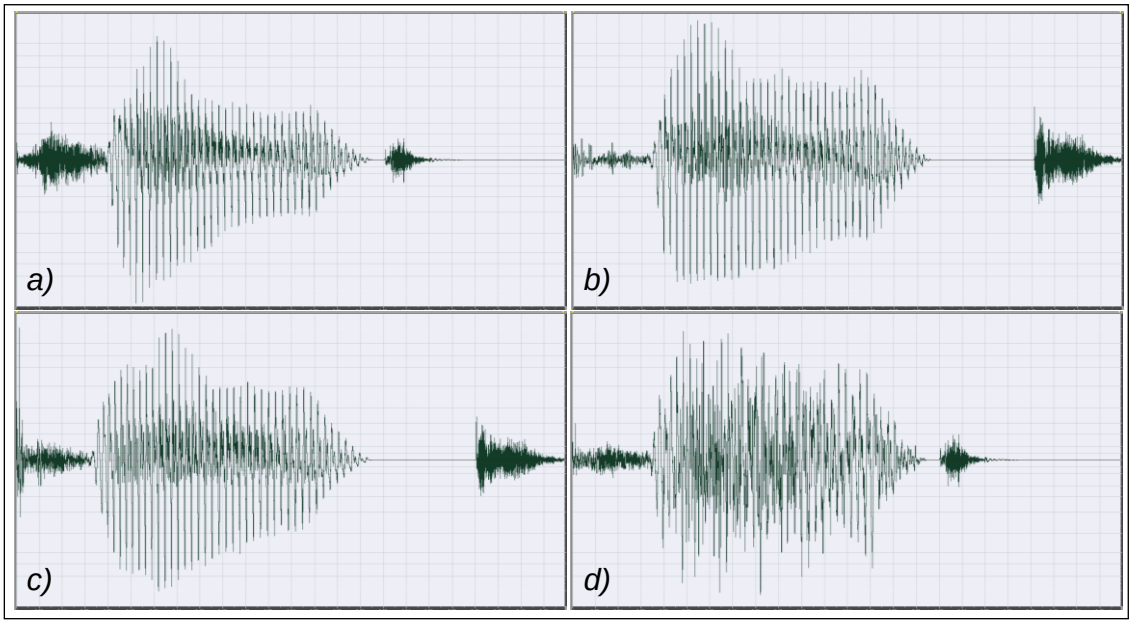


Figure 6.2: Example stimulus waveforms
a) tray /d/; b) kway /t/; c) play /t/; d)noise /d/

6.1.4 Data acquisition

MEG data acquisition, digitisation of HPI locations and headshape, and continuous head position monitoring were achieved with the same hardware and software as for the active paradigm. No EEG data were recorded.

6.1.5 Procedure

Prior to MEG recording, each participant had EOG, 2-lead ECG and HPI coils attached, and underwent head digitisation. After insertion of Etymotic earpieces, a brief hearing threshold check was performed in the MEG device. Visual impairment was corrected with non-magnetic lenses.

A film, without sound, was back-projected onto a screen and participants were asked to focus on watching the film and not pay attention to the auditory stimulation. Stimuli were passively presented in four separate blocks (one for each stem type) of

approximately 17 minutes duration, via non-magnetic earpieces. 1000 stimuli (800 standards and 100 of each deviant type) with 1s SOA were presented per block.

6.1.6 Data pre-processing

Maxfilter and ICA software were used to pre-process data in the same manner as used for the active memory paradigm, described in section 2.16. Using SPM5, a band-pass filter threshold of 0.5-44Hz was applied to the data and separate files were created such that epochs were aligned to the onset of the stems, or to the onset of the plosives (i.e. 320ms and 400ms post-stem onset for */d/* and */t/* respectively). This ensured equal baseline power (-50-0ms pre-plosive onset) across plosive-aligned conditions, minimising variation due to different stems and lags to plosive-onset, and possible effects of expectancy due to pattern regularity. See *Figure 6.3a* for visualisation of this alignment process. Data were split into separate magnetometer and gradiometer files and epochs in which MEG sensor values surpassed thresholds of 5000fT or 84000fT/m respectively, were rejected.

Stem-onset files were re-coded to indicate their position in the sequence, such that the first stem after a plosive-ending was '1', the stem preceding a plosive ending was '5' (for a */d/* plosive) or '6' (for a */t/* plosive) and intermediate stems were coded '2', '3', '4'.

To balance the amount of noise-related interference in stem-only and stem-plosive conditions, an equal number of stem-only and stem-plosive epochs were retained from all files prior to averaging, by pseudo-random retention of stem-only epochs from positions 2-4 (see above), such that an equivalent number were retained from the 1st and 2nd half of each block. Difference responses were computed for plosive-onset aligned epochs by subtracting stem-only epochs from stem-plosive epochs. Identical to the approach used with the active paradigm, for ROI-based analyses gradiometer RMS was computed upon the difference responses, whereas in sensor SPMs the RMS was contrasted between the original conditions.

6.1.7 Analyses

6.1.7.1 SNR

SNR was computed using mean global field power for each sensor type, in a similar manner to that used for the active paradigm. In this case, the averaged auditory N1m response to stems in each data block, excluding those which were preceded by a 'plosive' stimulus, was used as the signal measure. Standard deviation across sample points within

a 50ms window around the N1m (70-120ms) was divided by the standard deviation across a 50ms window in the baseline period (-50-0ms). Thus we obtained a measure of SNR for each data block. Our criterion for acceptable SNR was that no more than one data block per participant had SNR below 1.5. When this criterion was not met, all datasets from that participant were excluded from further analyses. It should be noted that this SNR estimate is not a pure indication of noise, since it only applies to the initial N1m response to auditory stimuli, which also might differ in true signal strength across blocks, individuals, or groups.

6.1.7.2 Whole-head analysis (difference responses)

Spatio-temporal regions of interest (ROIs) were defined from the main */d/* and */t/* difference responses (pooled across stem contexts) via identification of statistical maxima from 3D sensor SPMs. See *Figure 6.3* for diagrammatical explanation of how the difference responses were computed. Sensor SPMs were constructed using SPM5, in the same manner as for the active paradigm, described in chapter 2.

6.1.7.3 Single-channel analyses

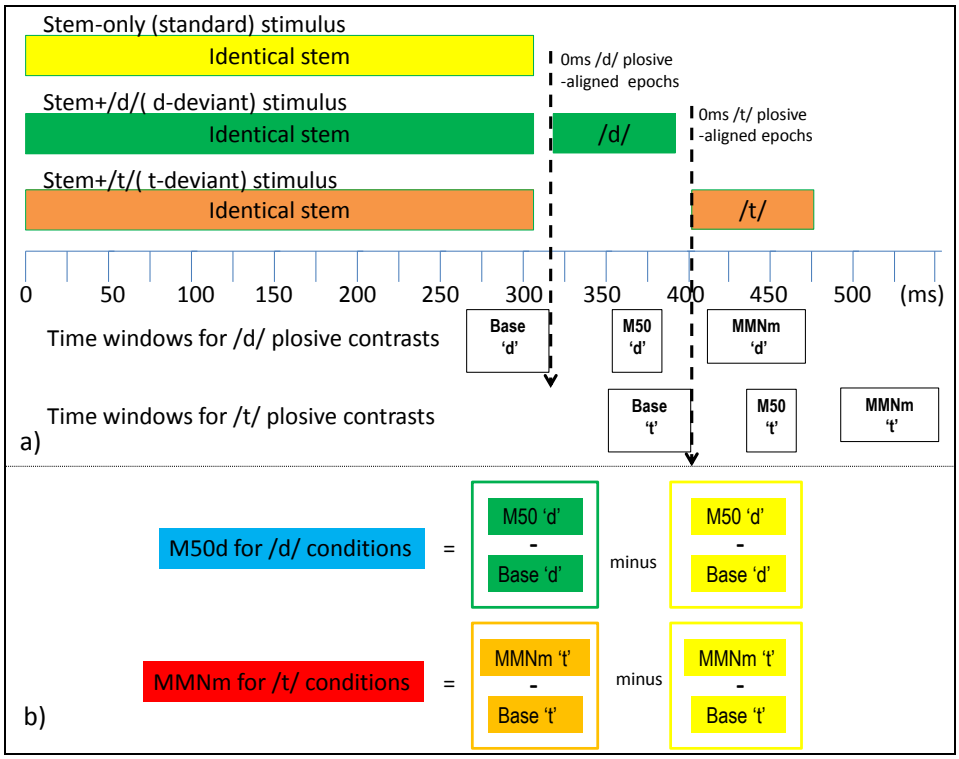


Figure 6.3: Computation of M50d and MMNm conditions

a) Depicts the relevant time periods during which stimuli occurred and that were used to attain the stem-only and stem+plosive baseline, M50 and MMNm response windows;
b) Illustrates subtractions of these basic responses used to compute M50d and MMNm conditions.

6.1.7.3.1 Latency

Fractional area latency (FAL) was used as a measure of latency and was computed as for the previously reported active memory paradigm. FAL was computed across windows of 30-70ms and 90-150ms for difference responses (referred to henceforth as M50d and MMNm respectively) at each ROI, chosen with reference to sensor SPMs and taking into account group average time courses. A slightly broader window was used to compute M50d FAL than magnitude in order to incorporate enough temporal variance to capture any significant latency differences between conditions. To identify any latency differences between conditions, 3-factor (stem x plosive x ROI) ANOVAs were conducted for each time window.

6.1.7.3.2 Magnitude of the difference responses

Mean effect magnitude at each ROI was computed (*see Figure 6.3b*) and more conventional analyses of variance were used to assess any interactions. Time windows used (defined from SPMs and time courses) were 35-65ms for M50d and 90-150ms for MMNm (*Figure 6.3a*). Difference in RMS power was used at gradiometer ROIs, whilst polarity was reversed for magnetometer ROIs in regions demonstrating negative flux to avoid effects of ROI in ANOVAs due to polarity differences (which does not provide information about location of sources of activity, see chapters 1 and 2). These data were input into 3-factor (stem x plosive x ROI) ANOVAs and follow-up t-tests were used to elucidate the nature of significant interactions.

6.1.7.3.3 Laterality Quotient (LQ)

To assess laterality in gradiometers, a normalised measure, the laterality quotient (LQ) was used to remove confounds associated with overall magnitude differences between conditions. LQ is the ratio of the magnitude difference between hemispheres divided by the sum of the magnitude from the 2 hemispheres: LQ=(Left-Right)/(Left+Right). In this case, mean RMS power of the difference response was taken as our measure for the ROI in each hemisphere. As LQ is a non-linear measure, a non-parametric test (Wilcoxon signed ranks) was used to compare LQ across conditions.

6.1.7.4 Whole-head analysis (stem-onset responses)

To check for potential confounds arising from the regularity of the stimulus pattern, sensor SPMs were used to contrast stem-onset epochs from positions 2-4 (stem-only stimuli) with those from position 5 or position 6 (stem+plosive stimuli). Stem-onset aligned epochs were entered into a 4(stems) x 3(plosive) factor 3D SPM design matrix and contrasts were made between the stem-only epochs and stem-plosive epochs for both plosive types and both sensor types. Small volume correction was used to examine the resultant SPMs for significant differences during time windows used for baseline correction in the plosive-aligned epochs, that is, 270-320ms (post-stem-onset) for */d/* and 340-400ms for */t/* plosives (*Figure 6.3a*).

6.2 Results

6.2.1 Signal-to-Noise Ratio (SNR)

One younger participant's gradiometer data were excluded, as SNR was below 1.5 for 3 of the 4 blocks. All participants' magnetometer data were retained, although one individual had SNR of 1.46 during one block (not the participant whose gradiometer data were excluded).

SNR was significantly higher for magnetometer than gradiometer data when all blocks were pooled together (*Gradiometers-Magnetometers: Z=-3.43, sig=.001*), see *Figure 6.4*. Data from both sensor types showed a main effect of block (*Gradiometers: F(1.73)=7.48, p=.004; Magnetometers: F(1.89)=13.7, p<.001*). Follow-up t-tests indicated that SNR was significantly higher for noise compared to the other 3 contexts (*Noise vs Word-like stems: Gradiometers: all t(16)>2.9, p<=.010; Magnetometers: all t(17)>3.7, p<=.002; Other comparisons: Gradiometers: all t(16)<2.1, p>=.06; Magnetometers: all t(17)<1.5, p>.15*), see *Figure 6.4*. These differences were driven by increased signal for the noise condition, rather than baseline differences (*Signal: Block: Gradiometers: F(1.80)=8.81, p=.001; Magnetometers: F(1.38)=12.5, p=.001; Baseline: Block: Gradiometers: F(3)=2.07, p>.1; Magnetometers: F(3)=0.983, p>.4*).

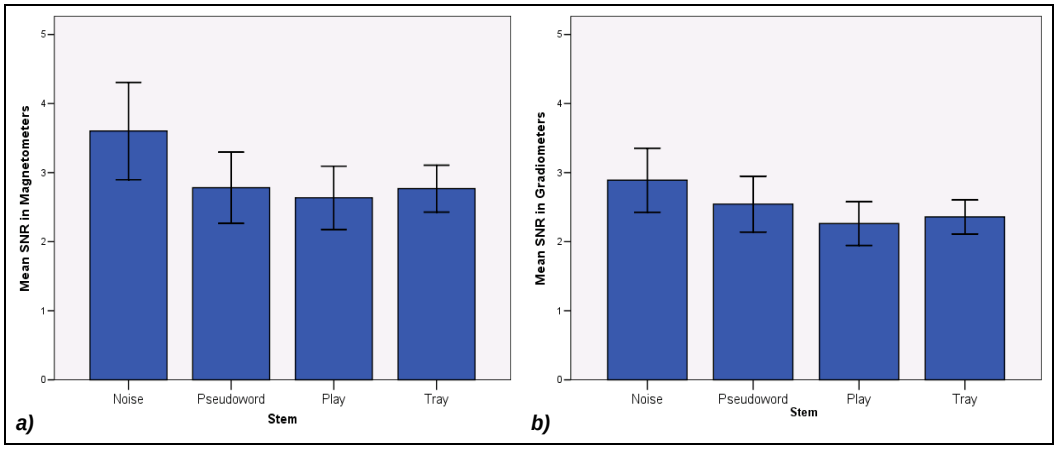


Figure 6.4: SNR according to block context
a) Magnetometers; b) Gradiometers. Error bars represent 95% confidence intervals.

6.2.2 Sensory gating

The corrected sensor SPMs showed no significant activation during the M50d time window, however, the uncorrected magnetometer sensor SPM (threshold at p=.001) for the difference response to */t/* plosives revealed 2 regions of significant effect over the left hemisphere, which were used to define regions of interest (ROIs). See *Figure 6.5c*. These regions were in an identical location to those identified for the MMNm response (see later), but reversed in polarity. Even without correction, no significant effects were evident for the difference response to */d/* at a threshold of p=.001. Pooled across ROIs, stems and plosive-type, mean M50d FAL in magnetometers was 49.9ms (SD=2.0ms), see *Figure 6.6a*. No ROIs were identified from gradiometer sensor SPMs within the M50d time frame, even at an uncorrected threshold of p=.01 (*Figures 6.5b&d*).

Figure 6.6b illustrates a non-significant trend towards an effect of ROI in the M50d in magnetometers (*F=3.48, p=.080*), reflecting a tendency towards larger magnitudes at the posterior temporal (MEG163m) than fronto-temporal (MEG021m) ROI.

6.2.3 Sensory memory (MMNm)

Magnetometer sensor SPMs (FWE-corrected for height at p<.05) for the main stem+plosive - stem-only difference contrast revealed significant bilateral responses from around 85-185ms for */d/* plosives and 90-300ms for */t/* plosives. Four ROIs located at the peak regions of activation were selected (fronto-temporal and posterior temporal locations bilaterally), see *Figures 6.5a&c*.

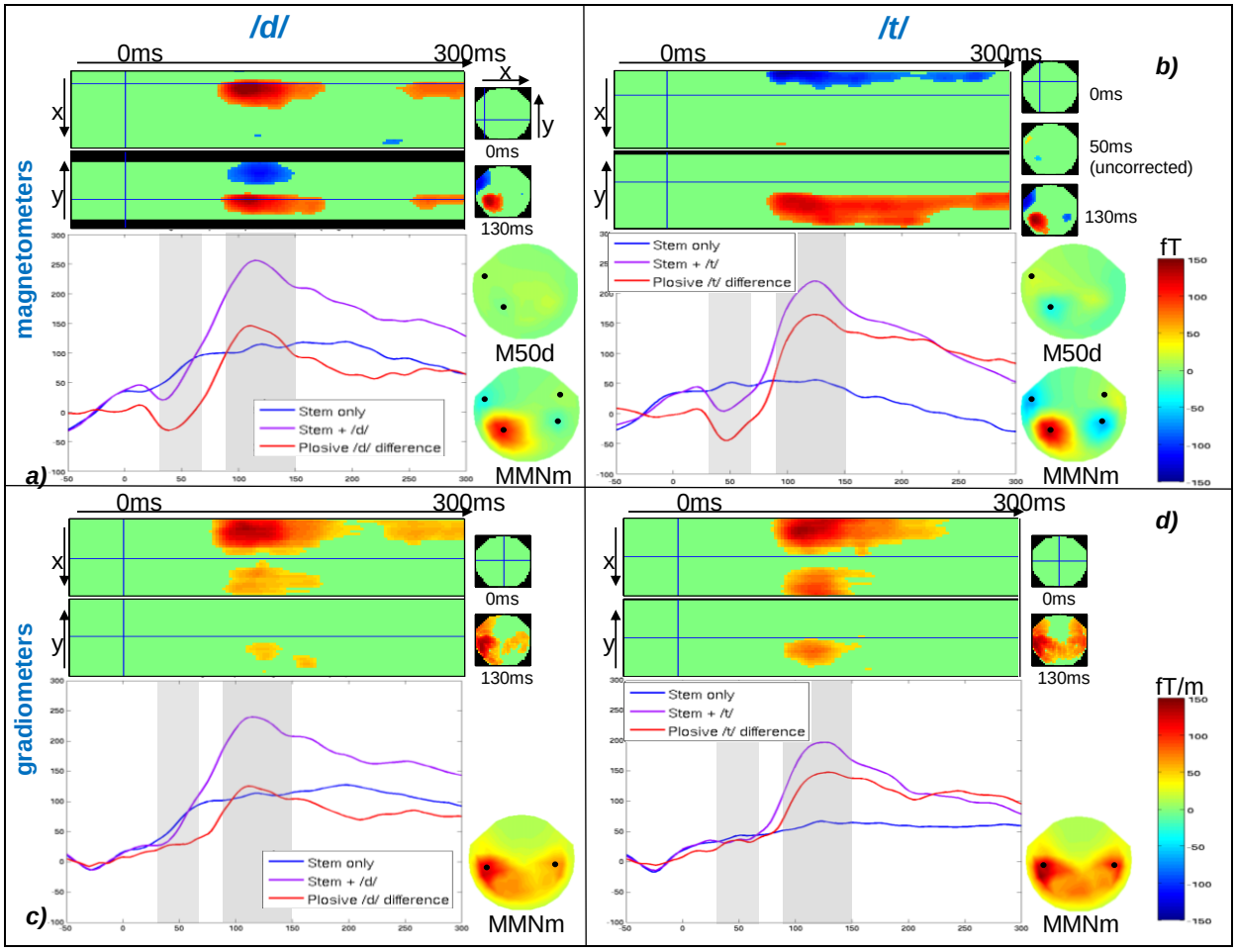


Figure 6.5: Difference responses to plosives, pooled across stem contexts
a) /d/ plosive in magnetometers; b) /t/ plosive in magnetometers;
c) /d/ plosive in gradiometers; d) /t/ plosive in gradiometers.
Within each box: Top: Sensor SPM from -50-300ms and snap-shot topographies; Bottom left: Time course from -50-300ms at maximal ROI (Magnetometers = left posterior temporal MEG163m; Gradiometers (RMS of difference) = left temporal MEG024g), shaded areas indicate time windows of interest; Bottom Right: Group average topographies across M50d window (35-65ms) & MMNm window (90-150ms), black circles indicate ROIs.

As evident in *Figures 6.5b&d*, gradiometer sensor SPMs revealed widespread significant difference responses, maximal over the left mid-temporal area. These began at around 80-90ms and persisted until 375ms for */d/* and 240ms for */t/*. Note that given the limited spatial extent of gradiometer sensitivity, thresholds for gradiometer SPMs (height at $p<.001$, uncorrected, and extent at $p<.05$, FWE-corrected), are more liberal than those for magnetometers. ROIs were identified from effect maxima, one over each hemisphere; these are highlighted in *Figures 6.5b&d*.

Mean MMNm FAL pooled across stem contexts was 130ms (SD=4.17ms) and 131ms (SD=5.3ms) in magnetometers and gradiometers respectively, see *Figures 6.7a & 6.8a*. FAL did not vary according to stem context, plosive or ROI in either sensor type.

In magnetometers, the ANOVA for response magnitudes revealed a main effect of ROI (*F(3)=16.1, p<.001*), such that the left posterior temporal ROI (MEG163g) displayed the largest MMNm.

6.2.4 Phonological processes

6.2.4.1 M50d

Despite the suggestion from *Figures 6.5a&c* of earlier /d/ than /t/ plosive M50d responses, FAL across the 30-70ms time window did not vary as a function of plosive-type, nor of stem or ROI (*All F<1.30, p>.28*). In terms of magnitude, a main effect of plosive-type was evident in magnetometers (*F=8.06, p=.011*), such that difference responses to /t/ were overall larger than those to /d/, see *Figure 6.6b*. The stem-only condition demonstrated significantly higher magnitude during the M50d window used for */d/* than */t/* plosive epochs (*/d/-/t/: t(17)=2.67, p=.016*).

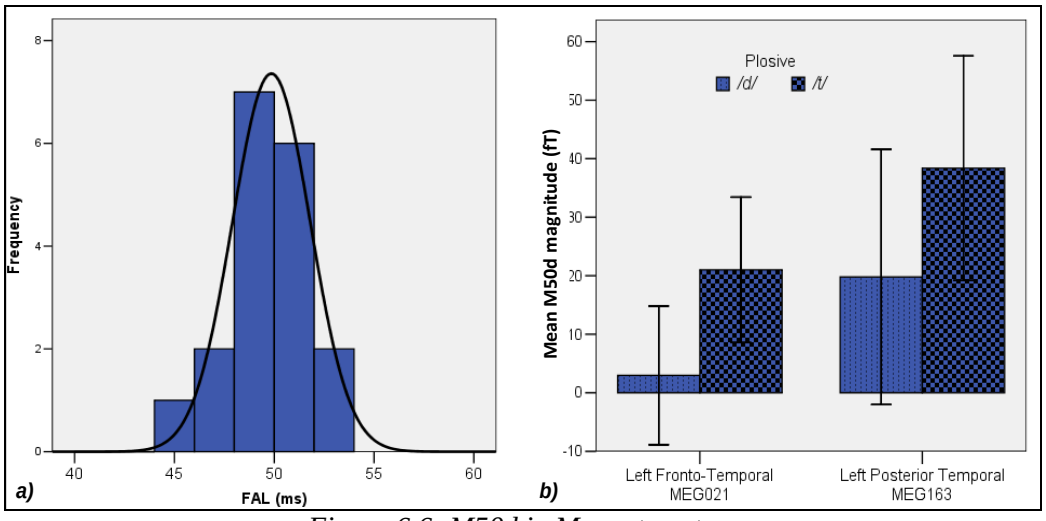


Figure 6.6: M50d in Magnetometers

a) Histogram depicts FAL, pooled across plosives, stems & ROIs; b) M50d magnitudes according to plosive type at each ROI, pooled across stems. Error bars represent 95% confidence intervals.

6.2.4.2 MMNm

Main effects of plosive were evident in magnitudes of MMNm responses in both magnetometers (*F=6.86, p=.019*) and gradiometers (*F=8.49, p=.010*), such that MMNm to */t/* plosives demonstrated consistently greater magnitude than that to */d/* plosives (*Pooled magnetometer ROIs: /t/-/d/: t(17)=2.62, p=.019*), see *Figures 6.7b & 6.8b*. The stem-only condition during the MMNm window for */d/* demonstrated higher ongoing activity than during the MMNm window for */t/* (*Magnetometers: F=20.2, p<.001; Gradiometers: F=22.7, p<.001*).

In gradiometers, a trend for interaction between plosive and hemisphere, such that MMNm evoked by */d/* plosives tended to be more left lateralised, was marginally significant (*F=4.44, p=.051*), see *Figure 6.8b*. There was no main effect of hemisphere during the respective MMNm time windows of the stem-only condition (*F=0.457, p>.5*).

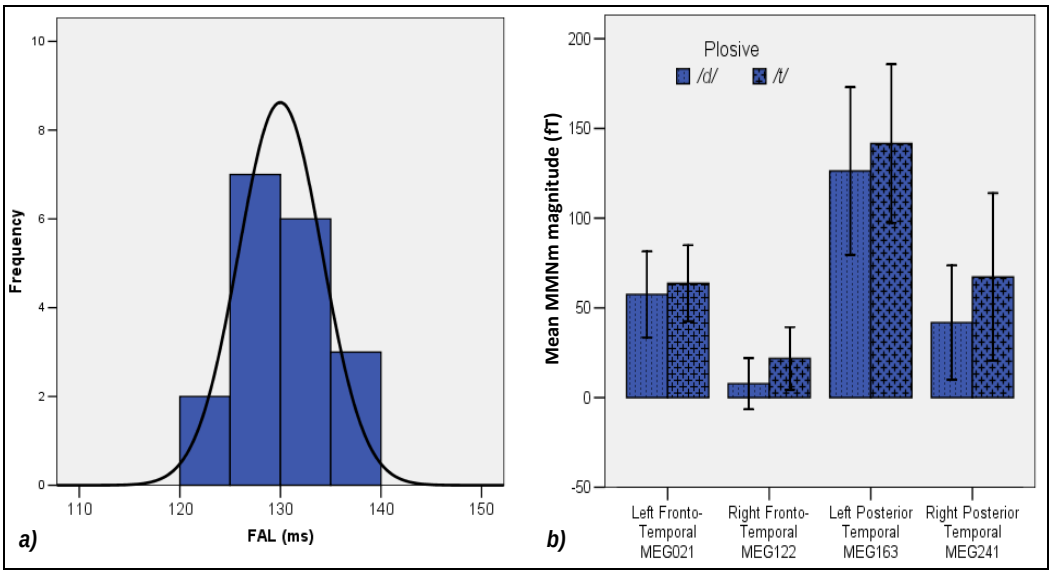


Figure 6.7: MMNm in Magnetometers

a) Histogram depicts FAL, pooled across plosives, stems & ROIs; b) MMNm magnitude according to plosive type at each ROI, pooled across stems. Error bars represent 95% confidence intervals.

6.2.5 Lexical/semantic processes

In both M50d and MMNm responses in both sensor types, neither FAL nor magnitudes demonstrated any significant main effects or interactions according to lexicality of stem context.

6.2.6 Morpho-syntactic processes

In gradiometers, a stem x hemisphere interaction for MMNm magnitude (*F(3)=2.86, p=.046*) reflected greater differential magnitude between hemispheres in '*play*' and pseudoword contexts (real and potential 'past' stem contexts) than in the context of '*tray*' or noise ('non-past') stems (*Left-Right: Past: both t(16)>=2.61, p<=.019; Non-past: both t(16)<=1.19, p>=.25*), see *Figure 6.8c.* LQ was computed for pooled 'past' and 'non-past' contexts. MMNm in 'past' stem contexts was significantly more left-lateralised for */d/* than */t/*, whereas this was not the case for 'non-past' contexts (*/d/-/t/: Past: Z=2.06, sig=.036; Non-past: Z=1.16, sig>.24*).

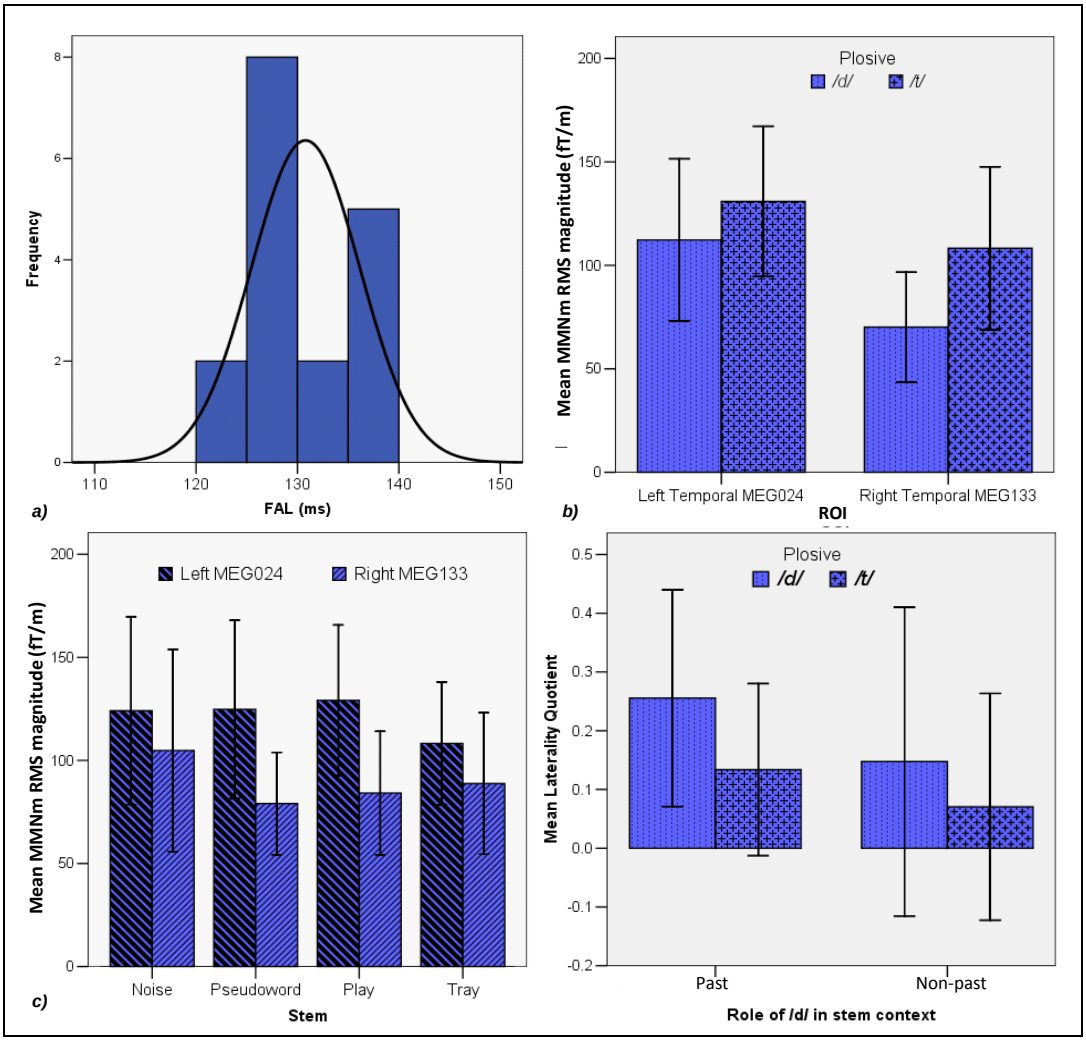


Figure 6.8 MMNm in Gradiometers

a) Histogram depicting FAL, pooled across plosives, stems & ROIs; b) MMNm magnitudes according to plosive type at each ROI, pooled across stems; c) MMNm magnitudes according to stem and ROI, pooled across plosive types; d) LQ for plosive type, pooled according to 'past' or 'non-past' stem contexts. Error bars represent 95% confidence intervals.

6.2.4 Stem onset-aligned epochs

Sensor SPMs revealed no significant differences between stem-plosive and stem-only epochs during the 50ms baseline periods preceding plosive onsets. Thus there was no evidence for a potential confound of baseline differences arising from the regularity of plosive occurrence.

6.3 Chapter Summary

A modified linguistic oddball paradigm was used to examine difference responses to plosive endings (*/d/* or */t/*) dependent upon the context established by frequent repetitions of the preceding stem. In achievement of our first aim, spatio-temporal regions of interest (ROIs) were defined for early automatic responses, that is, M50d, equivalent to a P50m

difference response, and magnetic mismatch negativity (MMNm), via statistical maxima in sensor SPMs.

6.3.1 Sensory gating (M50d) and sensory memory (MMNm)

M50d responses (*sensory gating*) were minimal within this group of younger participants and only left hemisphere magnetometer ROIs were defined, whereas MMNm (*sensory memory*) was far more prominent and we were able to define both gradiometer and magnetometer ROIs for this component of the difference responses (Aim 1). Gradiometer ROIs were in proximity to auditory cortex. ROIs were used to examine effects upon magnitude and latency of the different stem-plosive conditions.

6.3.2 Phonological/acoustic processes

Both M50d and MMNm displayed greater magnitude for */t/* than */d/* plosives (Aim 2); this was associated with smaller underlying stem-only responses during the equivalent time windows in the case of */t/* plosives (as the */t/* plosive onset, therefore M50d and MMNm time windows, occurred after a longer delay from stem-offset than the */d/* plosive onset).

A non-significant trend for MMNm to demonstrate greater */d/-/t/* difference over the right than left hemisphere (Aim 3) was not explicable in terms of any significant interactions of hemisphere and plosive in the stem-only condition.

6.3.3 Lexical/semantic processes

No significant differences were identified between responses in word and nonword contexts (Aims 2-3). This was contrary to extant literature, where left hemispheric enhancement of the MMNm response to words relative to pseudowords has been consistently reported.

6.3.4 Morpho-syntactic processes

Lateralisation of MMNm in gradiometers varied according to the potential role of */d/* as a regular past-tense grammatical suffix (Aim 3). Greater left-hemispheric magnitude advantage for responses to */d/* plosives existed for 'past' contexts where */d/* was a real or potential regular past tense grammatical suffix (pseudoword and '*play*') than where it was not (noise and '*tray*'). The potential confound of increased magnitude for */t/* responses

was subverted by computing the LQ, confirming significantly greater left lateralisation for */d/* than */t/* plosives only in 'past' contexts.

Chapter 7
Passive spoken word paradigm in healthy older controls

Chapter 6 explored the presence and spatio-temporal distribution in a young healthy population of MEG difference responses to plosive-endings in the context of word, pseudoword and noise stems. We identified two components of interest, M50d from 35-65ms (difference in the 'obligatory' auditory P50m response for deviant relative to standard stimuli) and MMNm from 90-150ms and assessed these effects upon latency, magnitude and laterality in the different conditions. The following chapter contrasts these findings with those from a group of neurologically healthy older people, who performed an identical MEG task and would later serve as an age-matched control group for clinical populations.

Aims & Predictions

Aim 1. Identify any impact of age upon main M50d and MMNm responses

In order to compare magnitude and topography of difference responses between groups, it was necessary to define time windows that captured equivalent portions of both M50d and MMNm responses across both age groups. With older age, increasing latency of difference responses in MMN paradigms has been reported albeit inconsistently (Amenedo & Diaz, 1998; Bertoli, et al., 2002; Schiff, et al., 2008). Any delays in FAL in older relative to younger groups would be evident as main group effects in the FAL ANOVAs.

Magnitude increase of basic P50(m) responses (Golob, et al., 2007; Pekkonen, et al., 1995; Soros, et al., 2009) and reduced P50 habituation (Patterson, et al., 2008) with age have been suggested to result from reduced cholinergic inhibitory activity (Pekkonen, et al., 2001; Pekkonen, et al., 2005). The minimum SOA of 5 seconds and mean of 10 seconds between identical plosives in our design optimised ability to detect M50d whilst avoiding habituation that occurs with shorter SOAs (Boutros, et al., 1995; Ermutlu, et al., 2007; Zouridakis & Boutros, 1992). In keeping with P50(m) literature, we expected to find a main effect of increased M50d magnitude in the older group.

Reduced MMN(m) amplitudes with increasing age (Czigler, et al., 1992; Kiang, et al., 2009; Schiff, et al., 2008) may be due to less efficient sensory memory representations. These cannot be accounted for by differences in the underlying N1(m)

response to auditory stimuli (Czigler, et al., 1992; Schiff, et al., 2008). We therefore anticipated smaller MMNm responses in the older than younger group.

Aim 2. Characterise interactions of age group with effects of stem and plosive

Although there have been several studies examining MMN(m) responses in ageing (Czigler, et al., 1992; Kiang, et al., 2009; Schiff, et al., 2008), none have manipulated linguistic variables. In healthy ageing, although deficits in language production have been reported, there is no behavioural evidence for receptive language deficits per se, for example both semantic priming and ability to detect misspellings are preserved (Burke & Mackay, 1997). Basic auditory N1m to speech-like stimuli and its habituation have been found not to change with age (Soros, et al., 2009). Thus it seemed unlikely that age group would influence modulation of MMNm responses according to either lexicality or potential grammatical role. A more prominent M50d response would make it easier to detect effects of linguistic variables upon this component; however, based on the previous literature, we did not specifically expect such an early component to be sensitive to features such as lexicality.

In relation to phonological/acoustic processes, any extant differences in response magnitude due to age may exacerbate differences in responses to */d/* versus */t/* plosives. Interactions of plosive-type and age-group during the M50d would be in keeping with a sensory gating function modulated by acoustic/phonological parameters, whereas we would expect that a decline in MMNm magnitude with age, related to impaired sensory memory, not to vary with plosive type.

Aim 3. Describe impact of age upon topographic properties of effects

Findings in the fMRI and PET literature (Cabeza, 2001; Dolcos, et al., 2002) suggest that older people tend to show more bilateral activation (i.e. reduced laterality) than their younger counterparts, potentially a sign of compensatory processes recruiting contra-lateral hemisphere. It may therefore be the case that such reduced laterality relative to younger individuals is evident in the main M50d and MMNm responses of the older group, and/or that laterality differences between plosives in ‘past’ stem contexts (that initiate grammatical processing), for example, are less evident in our older than younger sample. In comparing effects of laterality, the LQ controlled for overall magnitude differences between conditions and groups, making it a more sensitive measure to detect effects of age group upon laterality. However, as noted above, there is a dearth of

imaging studies manipulating linguistic variables that explore early cortical responses to language stimuli in older age, thus no firm predictions can be made. As there was no rostrality factor incorporated into gradiometer analyses (as we identified only one ROI per hemisphere for each response), the possibility of an anterior shift with ageing was not assessed in this analysis.

7.1 Method

7.1.1 Participants

Fifteen native English speakers, with a mean age of 67.2 years (SD=6.8 years) and who reported no neurological or psychiatric history, were either recruited from the MRC Cognition & Brain Sciences Unit volunteer panel, or were relatives of colleagues or other participants. All participants were right-handed, except for two, one of whom was left-handed and the other ambidextrous. All gave written informed consent and were paid for their participation. A subset of 7 participants had completed the ACE-R test battery as part of a separate study at the CBU and had given permission for that data to be used by other researchers. All scored within the normal range for age. These scores are not considered further here, but are depicted in illustrations of relationships between MEG and behavioural measures in chapter 9.

7.1.2 Procedure and pre-processing

The design, stimuli, procedure, data acquisition and data pre-processing were identical to those used with the younger group of participants (chapter 6). Computation of SNR was achieved in the same manner, with the same rejection criteria applied, as in chapter 6.

7.1.3 Analyses

7.1.3.1 Whole-head analysis (difference responses)

Spatio-temporal regions of interest (ROIs) for the main */d/* and */t/* difference responses (pooled across stem contexts) were identified in the same manner as for the younger group. The main */d/* and */t/* difference responses were contrasted between age groups via sensor SPMs in order to identify any significant group-related interactions beyond the ROIs already defined.

7.1.3.2 Single-channel analyses

7.1.3.2.1 Latency and magnitude of the difference responses

FAL and effect magnitude at each ROI were computed as detailed in the previous chapter. ANOVAs were used to detect effects of stem context, plosive, ROI or age group. T-tests were used to follow-up significant interactions.

7.1.3.2.2 Laterality Quotient (LQ)

LQ was computed in an identical manner to that used in the previous chapter. Non-parametric tests were used to compare LQ across conditions (Wilcoxon signed ranks) and between groups (Mann-Whitney test).

7.2 Results

7.2.1 SNR

All participants' data were retained in both sensor modalities, although one individual had SNR below 1.5 (1.49) for one block of gradiometer data. The lowest SNR during a single block for magnetometers was 1.68.

As was the case with the younger group, SNR was significantly higher for magnetometers than gradiometers (*Gradiometers-Magnetometers: Z=-2.50, sig=.012*), see *Figure 7.1a*-b. It did not significantly differ between groups when pooled across contexts (*Older-Young: Magnetometers: Z=1.09, sig>.28; Gradiometers: Z=1.19, sig>.24*), nor for any individual context (*Older-young: Magnetometers: all Z>-0.181<1.67, sig>=.10; Gradiometers: all Z<0.737, sig>.47*).

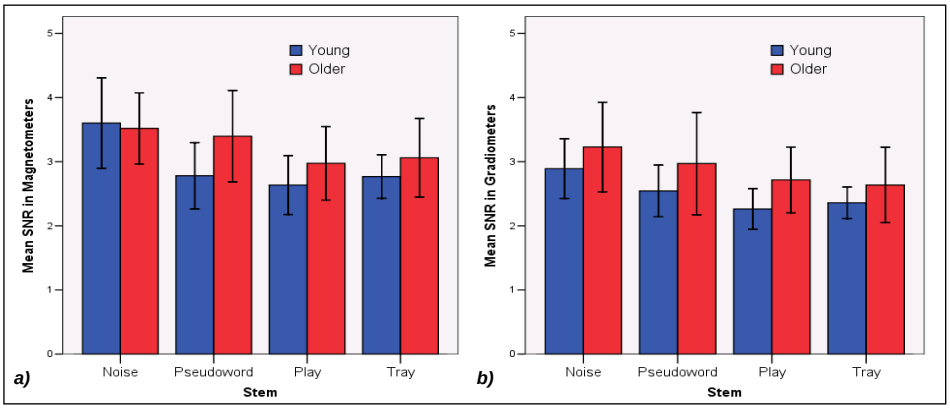


Figure 7.1: SNR according to block context

a) Magnetometers; b) Gradiometers. Error bars represent 95% confidence intervals.

7.2.2 Sensory gating

The older group sensor SPMs, time courses and topographies in *Figures 7.2a-d* illustrate the far more prominent M50d response, evident from around 45-60ms, in the older relative to younger group (although it was only the gradiometer response to */t/* plosives that survived the SPM FWE-correction for extent; *Figure 7.2d*). Sensor SPMs comparing age groups demonstrated main effects of group for both plosives and both sensor types, overlapping in time and sensor space with the main difference response. Four magnetometer and two gradiometer M50d ROIs were identified (*Figures 7.2a-d*), at identical sensors to those identified for MMNm responses in both participant groups (see later section and previous chapter). As more M50d ROIs were identified here than in the previous chapter, due to the more prominent response, we were able to proceed with more detailed analyses.

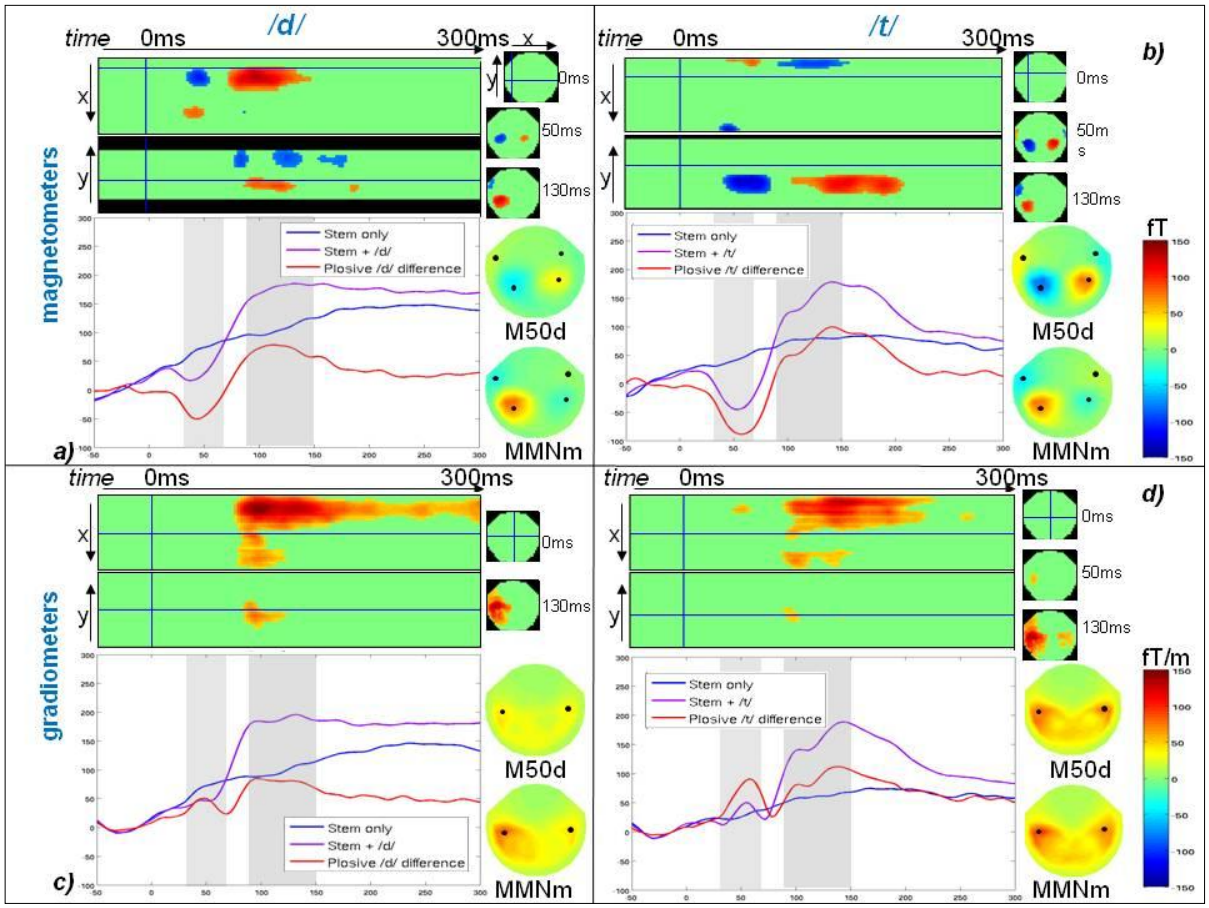


Figure 7.2: Difference responses to plosives, pooled across stem contexts
a) /d/ plosive in magnetometers; b) /t/ plosive in magnetometers;
c) /d/ plosive in gradiometers; d) /t/ plosive in gradiometers.
Within each box: Top: Sensor SPM from -50-300ms and snap-shot topographies; Bottom left: Time course from -50-300ms at maximal ROI (Magnetometers = left posterior temporal MEG163m; Gradiometers (RMS of difference) = left temporal MEG024g), shaded areas indicate time windows of interest; Bottom Right: Group average topographies across M50d window (35-65ms) & MMNm window (90-150ms), black circles indicate ROIs.

In magnetometers, FAL for M50d to */t/* plosives at the left posterior temporal ROI MEG163m (Mean=52.1ms, SD=3.0ms) was significantly later in older than younger participants (*Young-Older: t(29.5)=-2.71, p=.011*), with a mean delay of 3.6ms (SE=1.3ms), see *Figure 7.3a*. Given the absence of M50d to */d/* plosives in the younger group, age groups were not contrasted on this measure. Considering magnitude within the older group, there was a main effect of ROI (*F(1.77)=10.77, p=.001*), with maximal responses at left posterior temporal ROI MEG163m.

Between-group comparisons (using all 4 magnetometer ROIs and 2 gradiometer defined in this chapter) confirmed a main effect of age group in both magnetometers (*F=10.9, p=.002*) and gradiometers (*F=10.0, p=.004*), whereby higher M50d magnitudes were evident in the older group. In magnetometers, an interaction between group and ROI (*F(2.03)=4.98, p=.010*) indicated that inter-group magnitude differences were greatest at the maximal left posterior temporal ROI (MEG163m).

7.2.3 Sensory memory

The older group time courses in *Figures 7.2a-d*, particularly for /t/ plosives (*Figures 7.2b&d*), suggested a possible separation into 2 sub-components of the single peak evident during the MMNm time window for the younger group. Sensor SPMs for /d/ and /t/ plosive difference responses in the older group (*Figure 7.*2) and those examining main effect of age upon the difference response (not shown) indicated lesser MMNm magnitude in older compared to younger participants. Significant MMNm and age-related effects were restricted to areas where ROIs were defined for the younger group, thus the same ROIs (also identical to those defined for M50d responses) were used.

MMNm FAL (magnetometers mean=131.5ms, SD=4.9ms, pooled across stems, plosives and ROIs), did not significantly differ between older and younger participants, in magnetometers (*Young-Older: t(31)=-0.973, p>.33*) or gradiometers (*F<.001, p>.99*).

In support of SPM findings, ANOVAs upon MMNm magnitudes revealed a main effect of age (*F=4.75, p=.037*) in magnetometers and a marginally significant trend in gradiometers (*F=3.93, p=.057*), with smaller magnitudes in older participants, *Figures 7.5b-c, 7.6b*. Within the older group, the main effect of ROI seen in the young group magnetometer data (left posterior temporal maximal) persisted (*F(1.75)=7.74, p=.003*), *Figure 7.*5c. Similarly, a trend for a main effect of hemisphere in gradiometers (*F=4.12, p=.062*), with tendency for higher magnitude responses at the left than right temporal ROI, was observed.

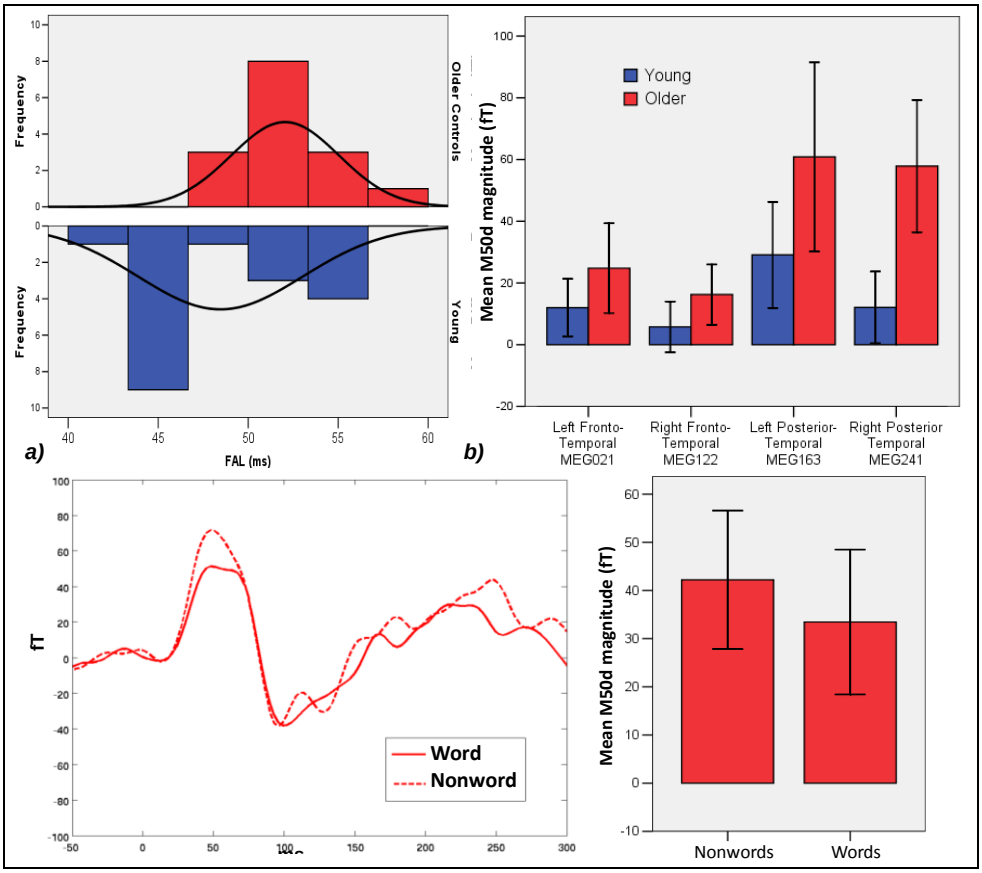


Figure 7.3: M50d in Magnetometers

a) FAL for /t/ plosives, pooled across stems at left posterior temporal ROI MEG163m; b) Mean magnitude of /t/-/d/ difference in M50d according to age group and ROI; c) Time courses of difference responses at right posterior temporal ROI MEG241m for word ('play' & 'tray') and nonword ('noise' & pseudoword) stem contexts; d) M50d magnitudes for word and nonword stem contexts, pooled across ROIs. Error bars represent 95% confidence intervals.

7.2.4 Phonological processes

7.2.4.1 M50d

FAL within the older group (pooled across ROIs) was significantly faster for */d/* (mean=48.9ms, SD=3.3ms) than */t/* (mean=52.2ms, SD=2.5ms) plosives in gradiometers (*/t/-/d/: t(14)=3.47, p=.004*), see *Figure 7.4a*. Likewise, in magnetometers there was a marginally significant main effect of plosive (*F=4.51, p=.052*) with mean delay of 2.0ms (SD=3.7ms) for */t/* relative to */d/* plosives.

Considering magnitude, as observed for the younger group, main effects of plosive occurred in magnetometers (*F=67.3, p<.001*) and gradiometers (*F=34.6, p<.001*), such that */t/* evoked bigger M50d responses than */d/*, *Figure 7.4b*.

An interaction of age group with plosive was evident in gradiometers (*F=19.7, p<.001*), whereby the */t/-/d/* difference was greatest within the older group, *Figure 7.4b*. In magnetometers, a 3-way interaction between group, ROI and plosive (*F(2.34)=3.12,*

p=.043) reflected that this older-group enhancement of the plosive-related difference occurred at posterior temporal ROIs only (*Younger-Older: /t/-/d/ posterior temporal: t(31)=-3.19, p=.003; /t/-/d/ fronto-temporal: t(31)=-1.02, p>.31*), *Figure 7.3b*.

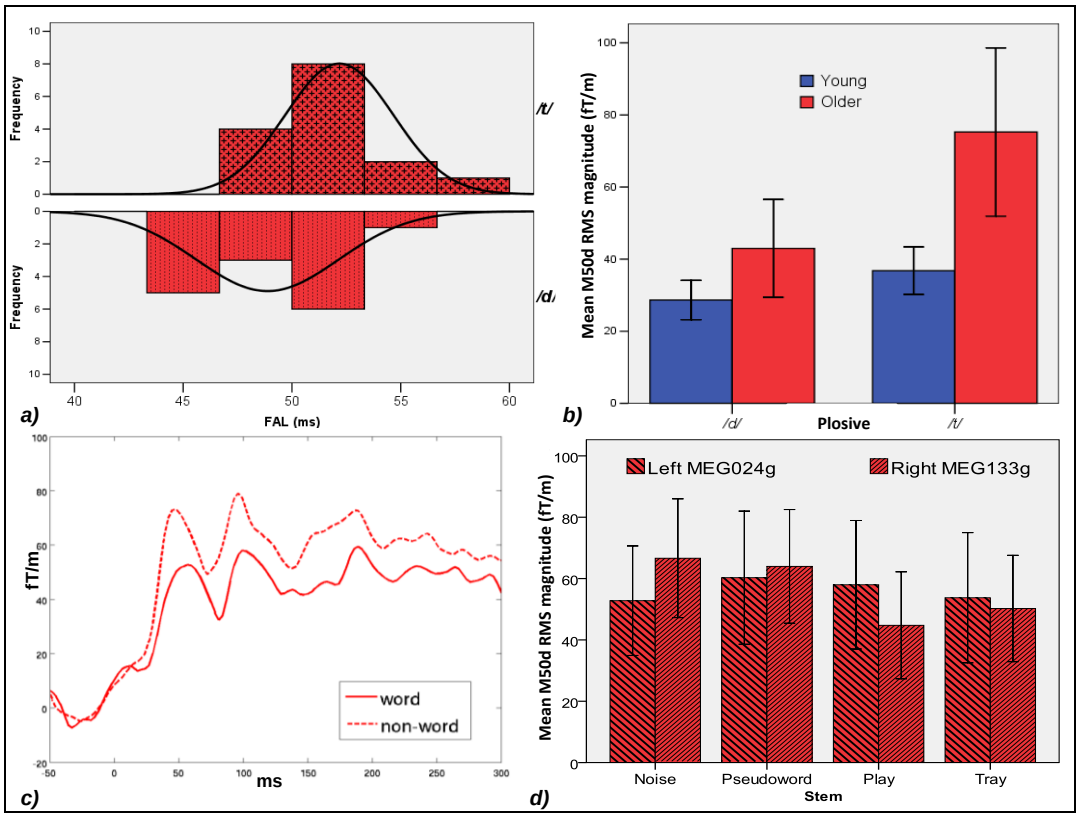


Figure 7.4: M50d in Gradiometers

a) FAL in older individuals according to plosive, pooled across stems & ROIs; b) M50d magnitude according to plosive & age group, pooled across stems & ROIs; c) Time courses of M50d at right temporal ROI MEG133g for word ('play' & 'tray') and nonword ('noise' & pseudoword) stem contexts; d) M50d magnitudes in older group according to stem context & hemisphere. Error bars represent 95% confidence intervals.

7.2.4.2 MMNm

In gradiometers, longer latencies for */t/* than */d/* plosives persisted for the older as for the young group, with mean FAL (pooled across stems and ROIs) of 133.4ms (SD=6.6ms) and 128.2ms (SD=6.5ms) for */t/* and */d/* respectively (*/t/-/d/: t(14)=3.88, p=.002*), see *Figure 7.6a*. In magnetometers, an interaction of plosive with ROI (*F(3)=2.99, p=.041*) revealed the same plosive-related latency difference (mean difference=7.5ms, SD=9.4ms) at the left posterior temporal ROI (MEG163m) only (*/t/-/d/: t(14)=3.09, p=.008*), see *Figure 7.5a*. Although this was not seen in the younger group, there was no significant group x plosive interaction at this ROI (*F=2.09, p>.15*).

A main effect of plosive in gradiometers (*F=13.1, p=.003*), such that MMNm responses to */t/* were greater than those to */d/*, replicated findings in the young group. The

main effects of plosive and age group did not interact, *Figure 7.6b*. However, in magnetometers, the difference in response magnitude according to plosive did not reach significance (*F=1.69, p>.21*), see *Figure 7.5b*.

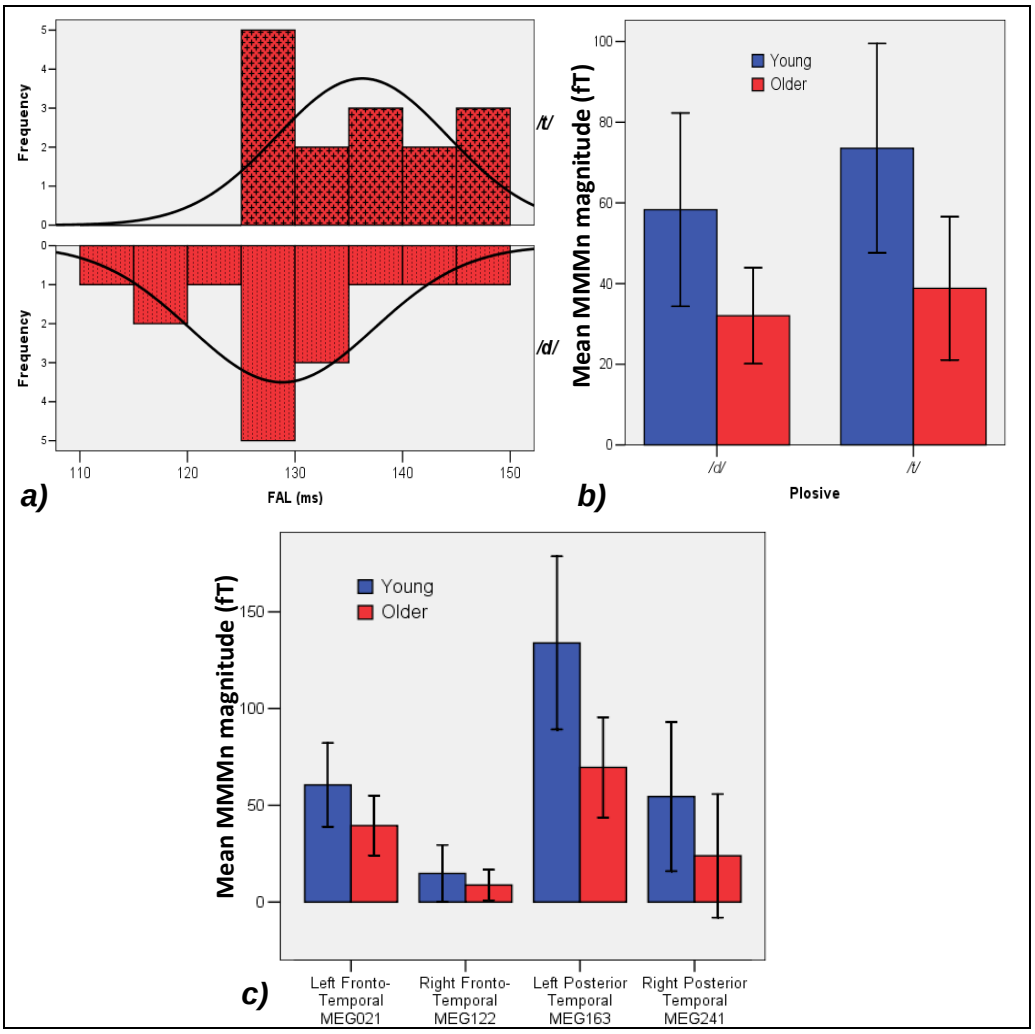


Figure 7.5: MMNm in Magnetometers

a) FAL in older group according to plosive, pooled across stems & ROIs;
b) Mean MMNm magnitude according to plosive & age group, pooled across stems & ROIs;
c) Mean MMNm magnitude according to ROI & age group, pooled across stems & plosives.
Error bars represent 95% confidence intervals.

7.2.5 Lexical/semantic processes

An unexpected main effect of stem in magnetometer data (*F(3)=3.19, p=.033*) indicated larger M50d in nonword (noise and pseudoword) relative to real word ('*play*' and '*tray*') contexts (*Nonword-Word: t(14)=3.46, p=.004*), *Figures 7.3c-d*. This effect was visually maximal at the right posterior temporal ROI (MEG241m, *Figure 7.3c*) but there was no interaction of stem with ROI. Stem-only responses during the M50d time windows revealed enhancement for '*play*' (a word stem) and reduction for 'noise' (a nonword

stem) at the left posterior temporal ROI (MEG163m) only, effects which were not able to account for the right hemisphere maximal nonword-word difference.

In gradiometers the main effect of stem (*F(3)=3.42, p=*.026) was accompanied by an interaction of stem with hemisphere (*F(3)=3.82, p=*.017), reflecting increased magnitude for nonword relative to word contexts at the right temporal ROI (MEG133g) only (*Nonword-Word: Left: t(14)=0.164, p>.87; Right: t(14)=3.50, p=.004*), *Figure 7.4c-d*. Indeed, LQ demonstrated differential lateralisation for nonword (RH>LH) and word (LH>RH) contexts (*Nonwords-Words: Z(15)=-2.06, sig=.040*). There were no significant lexicality differences in stem-only responses during the M50d window at the right temporal ROI (*Nonword-Word: t(14)=-1.16, p>.26*) or in the LQ (*Nonword-Word: Z(15)=-0.909, sig>.36*). Comparisons of LQ yielded no significant group differences in laterality for words (*Older-Young: Z(32)=0.283, sig>.79*), nonwords (*Older-Young: Z(32)=0.736, sig>.47*), or LQ of the difference between words and nonwords (*Older-Young: Z(32)=0.472, sig>.65*).

With regard to the MMNm responses, there were no main effects of, or interactions with, stem context in either sensor type. Within the older, like the younger group, LQ did not significantly differ between word and nonword stimuli (*Nonword-Word: Z(15)=-1.31, sig>.19*).

7.2.6 Morpho-syntactic processes

For MMNm magnitudes in gradiometers, a main effect of stem (*F(3)=4.71, p=.006*) was found to be due to smaller magnitude in '*tray*' compared to other stem contexts (*Pooled ROIs: Tray-Other: all t(14)>2.39, p<.032; Other pairwise comparisons: all t(14)<1.48, p>.22*). For clarification, we examined stem-only responses and found a main effect of stem (*F(3)=4.69, p=.006*) that reflected greater underlying activity in word relative to nonword contexts (*Words-Nonwords: t(14)=2.47, p=.027*). Further investigation in word contexts only, revealed smaller MMNm to */d/* but not */t/* plosives in the '*tray*' relative to '*play*' context, reaching significance at the left hemisphere ROI MEG024g only (*'play'-'tray': /d/: MEG024g: t(14)=2.39, p=.032; MEG133g: t(14)=1.85, p>.08; /t/: MEG024g: t(14)=1.54, p>.14; MEG133g: t(14)=0.101, p>.92*). There were no interactions of stem and plosive in magnetometer data for the MMNm responses.

Higher LQ, signifying greater left lateralisation, for MMNm to */d/* than */t/* plosives in 'past' stem contexts was replicated in the older group (*/d/- /t/: Past: Z=2.05, sig=.041;*

Non-past: Z=0.852, sig>.39), see *Figure 7.6d*. LQ did not differ between groups for */d/* or */t/* in any stem context (*Young-Older: all Z<1.14, sig>0.24*).

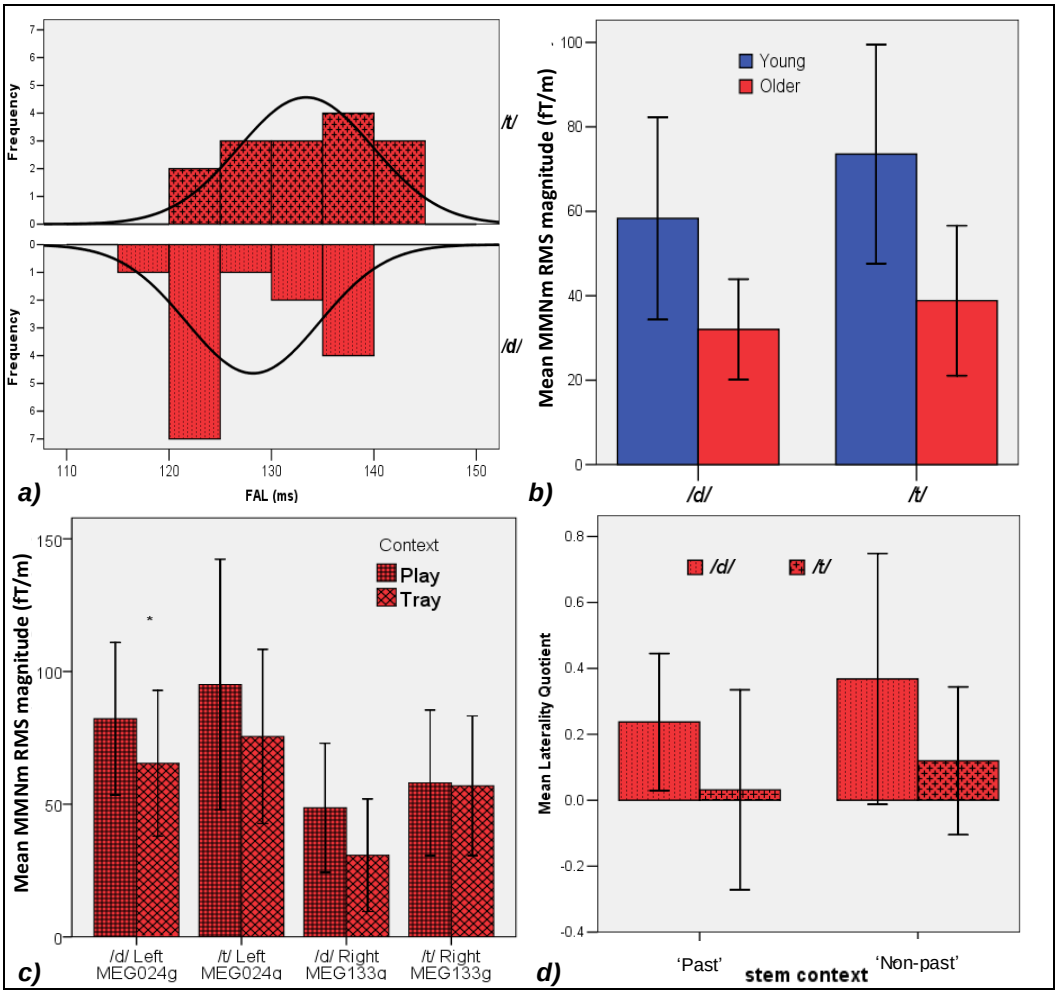


Figure 7.6: MMNm in Gradiometers

a) Histogram depicts FAL in older group according to plosive, pooled stems & ROIs; b) MMNm magnitude according to age group & plosive type at each ROI; c) MMNm magnitude in word contexts according to plosive and ROI; d) LQ for plosive type, according to 'past' or 'non-past' stem context. Error bars represent 95% confidence intervals.

7.3 Chapter summary

Our passive linguistic oddball paradigm was replicated in a group of neurologically healthy older individuals, in order to explore effects of older age upon M50d (difference response related to P50m obligatory auditory response) and MMNm responses evoked by several stimulus conditions, and to accrue control data upon which to base subsequent comparisons with dementia patients.

The same analysis steps were followed as for the younger group discussed in the previous chapter, with additional comparisons made between age groups. Identical ROIs were identified for both age groups in most analyses, albeit additional ROIs were located for the M50d within the older age group. These were used to extract data on latency,

magnitude, and laterality that were utilised to explore effects associated with sensory gating, sensory memory, phonological/acoustic processes, lexical/semantic processes and morpho-syntactic processes. The main findings are summarised below and listed in *Table 7.1*.

Table 7.1: Significant passive paradigm effects in older group

Effect (measure)	Conditions	ROIs
Sensory gating (M50d magnitude)	Older > Young	Magnetometer MEG163 Gradiometers pooled
Sensory gating (M50d FAL)	Older > Young	Magnetometer MEG163
Sensory memory (MMNm magnitude)	Older < Young	Magnetometers pooled
Phonological/acoustic (M50d magnitude)	*/t/ > /d/* (older > young)	Magnetometers MEG163m & MEG241m Gradiometers pooled
Phonological/acoustic (MMNm magnitude)	*/t/ > /d/*	Gradiometers pooled
Phonological/acoustic (M50d FAL)	*/t/ > /d/*	Magnetometers pooled Gradiometers pooled
Phonological/acoustic (MMNm FAL)	*/t/ > /d/*	Magnetometrer MEG163m Gradiometers pooled
Lexical / semantic (M50d magnitude)	Nonwords > Words	Gradiometer MEG133g Magnetometers pooled
Lexical / semantic (M50d LQ)	Words > Nonwords (words more left lateralised)	Gradiometers MEG024g & MEG133g
Morpho-syntactic (MMNm LQ)	*/d/ > /t/* in 'past' contexts (*/d/* more left lateralised)	Gradiometers MEG024g & MEG133g
Morpho-syntactic (MMNm magnitude)	'*played*' > '*trade*'	Gradiometer MEG024g

7.3.1 Sensory gating (M50d)

M50d responses were significantly more prominent in older than younger participants (Aim 1). There was a small (~3ms) but significant delay in the M50d response latency for

the older relative to younger group (Aim 1), which did not interact with any of the conditions (Aim 2). It was felt unnecessary to adjust the comparatively large (30ms) analysis time window to account for such a small latency difference.

7.3.2 Sensory memory (MMNm)

Magnitude of the MMNm was significantly smaller in older participants across both sensor types (Aim 1). Latency did not differ between age groups, despite the possible appearance of 2 overlapping sub-components in the older group average occurring in place of what appeared as a single component in the younger group average.

7.3.3 Phonological/acoustic processes

The relative magnitude increase of responses to */t/* compared to */d/* plosives was enhanced in the older group during the M50d time window (Aim 2). The */t/-/d/* magnitude difference remained significant during the MMNm in gradiometers, but there was no enhancement of the effect with older age (Aim 2).

Associated with their more defined peaks, latencies of responses to */t/* plosives were longer than those to /d/ for both M50d and MMNm. This was not seen in the younger group (where plosive modulation of FAL was examined only for MMNm) but there was no evidence of significant age-related variation in this effect (Aim 2).

7.3.4 Lexical/semantic processes

In the older, but not younger, group, effects related to lexicality were evident in the M50d, but not MMNm. Nonword stems ('noise' and pseudoword) evoked higher magnitude M50d responses than word stems in both sensor types, an effect which could not be accounted for by underlying stem-only responses (Aim 2). In gradiometers this occurred at the right temporal ROI only. Laterality analyses confirmed that nonword contexts showed relatively greater right lateralisation / reduced left lateralisation compared to word contexts (Aim 3).

7.3.5 Morpho-syntactic processes

Whilst an interaction of stem and hemisphere was not evident in the MMNm responses of the older group, the finding of greater left lateralisation, using a normalised measure of laterality, for */d/* than */t/* in 'past' contexts where */d/* was a real or potential grammatical suffix, was replicated (Aim 3). When comparing word contexts only, MMNm responses

to '*played*' (where */d/* was a past-tense suffix) were greater in magnitude than those to '*trade*' (a morphological twin where */d/* had no grammatical function); this effect was significant over the left hemisphere only (Aim 3).

Chapter 8

Passive spoken word paradigm in probable Alzheimer's disease patients

Chapter 7 explored the impact of older age upon the M50d, akin to the 'obligatory' P50m auditory response to deviant stimuli minus ongoing activity in response to stem-only stimuli, and the MMNm, within a modified version of a passive spoken word oddball paradigm. Spatio-temporal ROIs were defined and used to examine variation in responses to different plosive-endings in contexts of different word and nonword stems, to probe different levels of speech information processing.

With a view to detecting measures that could reliably distinguish between dementia patients and controls, the following chapter sought to identify significant differences in MEG responses acquired via an identical paradigm, between these healthy age-matched controls (control group) and a group of patients diagnosed with probable mild Alzheimer's disease (pAD).

Aims and predictions:

Aim 1. Describe impact of dementia upon effects of interest

Our first aim was to identify measures relating to our effects of interest upon which the pAD and control groups differed. The differences we predicted were as follows:

Sensory gating: An increase in M50d magnitudes in patients relative to controls was expected, as reduced sensory gating, that is, lesser decrement in P50(m) magnitude when an auditory stimulus is repeated, has been reported in patients with Alzheimer's disease relative to elderly controls (Golob, et al., 2001; Jessen, et al., 2001; Thomas, et al., 2010) and shown to correlate with overall cognitive functioning and tasks requiring executive control (such as verbal fluency and backwards digit span), but not with episodic memory or visuo-spatial function (Thomas, et al., 2010). Previous studies do not unambiguously predict any group-related M50d latency differences in the current paradigm, but differences in FAL could result from magnitude increases.

Sensory memory: MMN(m) magnitude decreases in patients with pAD as inter-stimulus interval (ISI) increases (Pekkonen, et al., 1994; Yokoyama, et al., 1995), whilst no decrement relative to controls is reliably present at ISIs of 1 second and below (Bronnick, et al., 2008; Gaeta, et al., 1999; Kazmerski, et al., 1997). These findings have been interpreted as evidence of a more rapid decay of memory representations than in healthy

age-matched controls, rather than impairment in change detection per se (Pekkonen, 2000; Pekkonen, et al., 1994). Disruption of central cholinergic activity has been shown to reduce MMN magnitude, and was proposed to contribute to faster sensory memory decay in pAD (Pekkonen, et al., 2001). Given the 1 second ISI in the current paradigm, a reduction in MMNm magnitude relative to age-matched controls might not be easily seen, however the salient acoustic contrasts used here may provide increased signal-to-noise ratio, enabling more subtle decrements to become evident.

Phonological processes: No studies have so far reported differential processing specific to phonology in patients with AD relative to controls; specifically, there are no reports of diminished capacity to process regular past-tense verb forms, unlike the phonologically-driven difficulties observed in non-fluent aphasia for example (Bird, et al., 2003). Consequentially no group differences were anticipated in the differential laterality of MMNm for */d/* relative to */t/* plosives in 'past' contexts. It was however anticipated that enhanced M50d magnitudes in the pAD group might be associated with exacerbation of plosive-related differences associated with phonological/acoustic salience.

Lexical/semantic processes: Semantic deficits are reported to occur early but perhaps not uniformly in the course of pAD (Adlam, et al., 2006; Dudas, Clague, et al., 2005; Perry, et al., 2000) and are likely due to both degraded semantic representations and inefficiencies in lexical retrieval (Chertkow & Bub, 1990; Rogers & Friedman, 2008). Given such deficits, we predicted that lexicality ('wordness') differences in magnitude and laterality found in controls would be reduced or absent in the patient group.

Morpho-syntactic processes: Increased errors in generation of irregular relative to regular past-tense verbs from their present tense occur to a disproportionate extent in patients with probable Alzheimer's disease (Ullman, et al., 1997). Although initially attributed to diminished semantic representations, this 'regularity' factor was confounded with differences in neighbourhood consistency; that is, whether other stems in the phonological neighbourhood mostly have past-tense forms that are similar to and assist production of the past tense of that stem ('friends', e.g. match-matched, hatch-hatched, latch-latched, patch-patched) or mostly have rather different past-tense forms that interfere with correct past-tense production ('enemies', e.g. fit-fitted, knit-knitted, but hit-hit and spit-spat,). A comparison which crossed consistency and regularity found that the higher error rate in individuals with pAD relative to controls was accounted for to a large extent by summed lexical frequency of enemies, a pattern of errors qualitatively different

from that in semantic dementia patients with a primary semantic deficit (Cortese, Balota, Sergent-Marshall, Buckner, & Gold, 2006). This difficulty in resolving interference from 'inconsistent' neighbours was attributed to a problem with inhibiting processing of distracters. Given these findings, we anticipated reduced efficiency in processing the inconsistent 'trade', in that it would be necessary to suppress its incorrect interpretation as the past tense of '*tray*' (i.e. '*trayed*').

Aim 2. Identify metrics that reliably discriminate pAD patients and controls

As was the case with the active paradigm, we aimed to devise a MEG metric, based upon measures identified as differing between patient and control groups, able to predict diagnostic category. As acknowledged in chapter 4, there is a bias towards above chance performance for these metrics, given that they were both devised and tested within the same groups and that there is circularity in computing sensitivity and specificity for measures selected on the basis that they significantly differed between these groups. However, the pAD patients in the present chapter constituted a 'training' dataset from which to derive classification methods, which were later applied to a separate larger group in chapter 9.

In replication of the methods employed in chapter 4, we computed 10th percentile and logistic regression metrics. In divergence from the 10th percentile approach in chapter 4 (where one measure for each effect was used to compose a single metric), given that some effects examined in the current chapter were novel and that more than one measure of each effect had sensitivity at or above 50%, we created multiple metrics that reflected sensory gating, sensory memory and linguistic (i.e. lexical and/or morpho-syntactic) effects, in addition to a 'combined metric' that summed all of these measures. Logistic regression offered the possibility to derive a metric that can be used to predict the probability of an individual having dementia. As in chapter 4, we used a backwards step-wise procedure and first computed a model for each effect of interest separately, then combined all predictor variables retained in the individual effect of interest models in an effort to arrive at the most parsimonious solution.

8.1 Method

8.1.1 Participants

The same 8 individuals (6 males) with a diagnosis of mild pAD who participated in the active paradigm, returned on a second occasion to participate in the current experiment.

All were right-handed and ranged in age from 60 to 80 years with a mean age of 71.2 years (SD=7.8 years). Age of the pAD group did not significantly differ from that of the control group (*t(21)=1.28, p>.21*).

This experiment was approved by a local NHS research ethics committee (LREC code: 08/H0306/68) in conjunction with the experiment reported in chapters 4-5. Participants gave written informed consent. They were not paid for their participation, but received reimbursement for travel expenses.

8.1.2 Procedure, pre-processing and SNR

The design, stimuli and procedure were identical to those used with the control groups (chapters 6-7). Data were recorded and pre-processed in an identical manner as for the control groups. SNR was computed in an identical manner to that used in the previous chapter and the same rejection criteria were used.

8.1.3 Analyses

8.1.3.1 Analyses of magnitude, latency and laterality

As ROIs and time windows were defined *a priori* based on data reported earlier in chapters 6-7, no whole-head analyses were conducted for the patient group, although topographies depicting group mean effects of plosive and time courses from maximal ROIs were visually inspected and are provided for illustrative purposes.

Magnitude, FAL and LQ were computed as in previous chapters. For magnitude and latency, ANOVAs were used to assess main effects of group or interactions with other factors and followed up with t-tests. Effects identified previously in the control group were directly contrasted between groups via t-tests. For LQ, only significant effects in the control group were directly examined in the patient group. As LQ is a non-linear measure, non-parametric tests were used to compare LQ across conditions and between groups (Wilcoxon signed ranks and Mann-Whitney tests, respectively). In order to maximise ability to detect group differences, which were subsequently assessed for sensitivity to pAD, multiple comparisons were not corrected for at this stage.

8.1.3.2 10^{th} percentile thresholds

In the same manner as described in chapter 4, for each measure identified as differing significantly between pAD and control groups, the control group's 10^{th}/90^{th} percentile (according to the direction of the difference) was computed. Individual data points that

fell beyond the cut-off threshold were classified as 'abnormal'. Measures with sensitivity to pAD of 50% or above were selected for inclusion in an 'abnormal' measures count. We computed 3 separate counts; these were for sensory gating (main M50d), sensory memory (main MMNm) and linguistic (combination of lexical and morpho-syntactic) effects. Finally a combined count was computed for each participant. These counts were contrasted according to group to identify the threshold number of 'abnormal' measures that optimised sensitivity and specificity to the diagnosis of pAD.

8.1.3.3 Logistic regression

Backwards step-wise logistic regression analyses with group (pAD or control) as the dependent outcome variable proceeded in a similar manner to that described in chapter 4. Initially, separate models were created using predictor variables that reflected different effects of interest. All predictor variables that were retained in these individual models were combined into a single model and a backwards step-wise procedure was applied. As perfect separation of the groups prevented a single combined solution from being reached, we constructed two independent LR models in order that they could subsequently be used to predict probability of dementia in an independent group. One model was based upon sensory gating and sensory memory ('sensory') predictor variables and the other combined lexical and morpho-syntactic ('linguistic') predictors. Statistical measures (listed in chapter 4) were consulted to assess the validity of each of these models.

8.2 Results

8.2.1 SNR

No pAD group data were excluded, although one individual had SNR of 1.46 for one block of gradiometer data. The lowest SNR during a single block for magnetometers was 1.53.

Unlike controls, higher SNR in magnetometers than gradiometers did not reach significance within the pAD group (*Magnetometers-Gradiometers: Z=1.68, sig=.093*), see *Figure 8.1a*-b. Despite the appearance of overall lower SNR in the pAD group (*Figures 8.1a*-b), this group difference reached significance only for the pseudoword context in magnetometers (*control-pAD: Z=-2.07, sig=.040*). SNR did not significantly differ between groups when pooled across blocks (control-*pAD: Magnetometers: Z=-1.68, sig>.10; Gradiometers: Z=-1.61, sig>.11*).

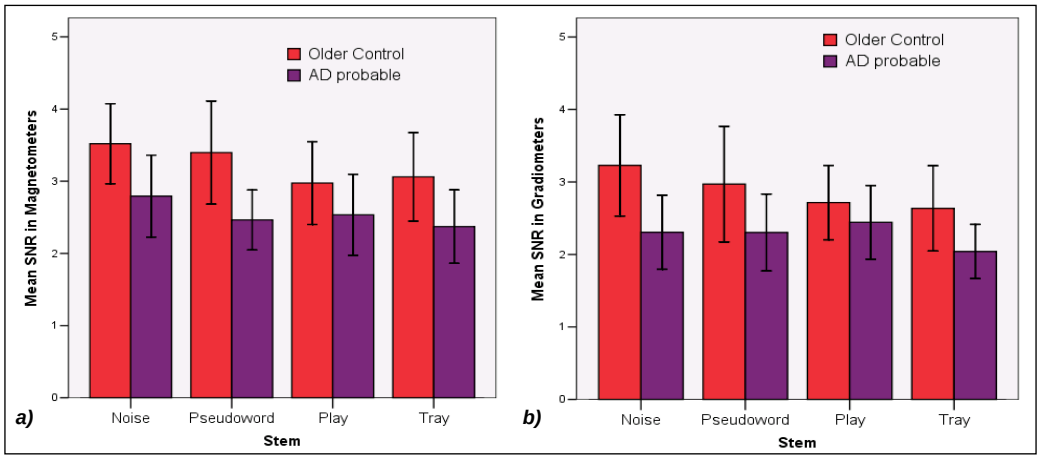


Figure 8.1: SNR according to stem context for pAD and control groups
a) Magnetometers; b) Gradiometers. Error bars represent 95% confidence intervals.

8.2.2 Sensory gating (M50d)

Time-courses and topographies of main difference responses according to plosive and sensor type are presented in *Figures 8.2a-d*. ROI locations are indicated for reference.

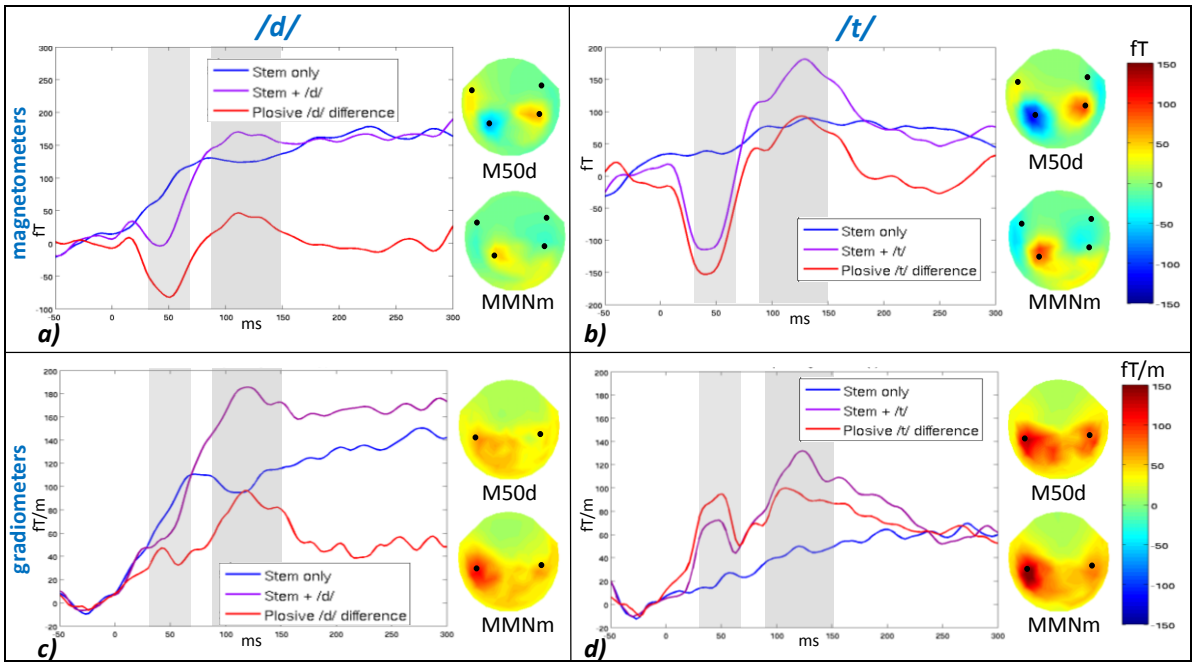


Figure 8.2: pAD group mean difference responses to plosives, pooled across stem contexts
a) /d/ plosive in magnetometers; b) /t/ plosive in magnetometers;
c) /d/ plosive in gradiometers; d) /t/ plosive in gradiometers.
Within each box: Left: Group mean time course from -50-300ms at maximal ROI, shaded areas indicate time windows of interest (Magnetometers = left posterior temporal MEG163m; Gradiometers RMS of difference = left temporal MEG024g); Right: Group average topographies across M50d window (35-65ms) & MMNm window (90-150ms), black circles indicate ROIs.

The right fronto-temporal magnetometer ROI MEG122m was excluded from FAL analyses, as there was no significant M50d present here in the pAD group. A main effect of group (*F=8.35, p=.009*) in gradiometer data reflected earlier M50d FAL in the pAD

relative to control group, by a mean of 2.7ms (SE=0.9ms), see *Figures 8.2c-d*. M50d FAL pooled from both ROIs (MEG024 and MEG133) was thus retained for further analyses. There was no main effect of group in magnetometer FAL data (*F=1.66, p*>.21). However an interaction of group and stem context (*F=2.90, p=.042*) reflected a tendency for faster M50d in the pAD relative to control group, with the exception of 'noise' contexts where the difference was in the opposite direction, see *Figure 8.3c*. None of these group differences reached significance at the level of individual stem context (*Tray: F=4.11, p=.055; Other contexts: F<2.51, p>.13*).

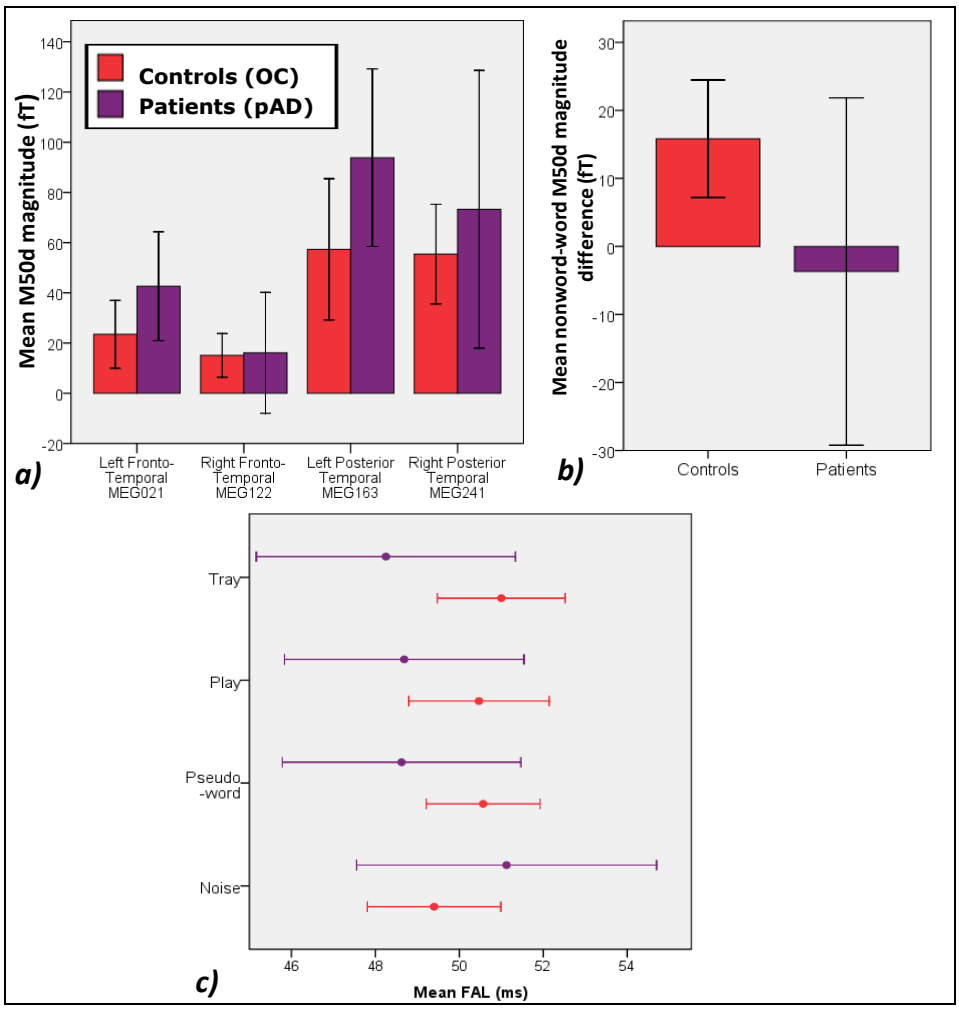


Figure 8.3: M50d in Magnetometers

a) Mean M50d magnitude according to group at each ROI; b) Mean M50d magnitude difference for nonword – word contexts at MEG241m, according to group; c) FAL according to group and stem, pooled across ROIs & plosives. Error bars indicate 95% confidence intervals.

In terms of magnitude, as evident in *Figures 8.3a & 8.4b*, there was high variability within the pAD group. A main effect of ROI in magnetometers (*F(3)=7.91, p=.001*) reflected that largest responses were detected at posterior ROIs. Magnitude in magnetometers was significantly increased relative to controls at both left hemisphere

ROIs (p*AD-control: MEG021m: t(21)=1.76, p=.045; MEG163m: t(21)=1.32, p=.050*) and these ROIs were retained for use in further analyses. The tendency for greater M50d magnitude in pAD relative to control groups was present in mean gradiometer responses (*Figure 8.4b*) but not statistically significant (*F=1.94, p>.2*), possibly due to large overall variability in responses within the pAD group and small sample size.

8.2.3 Sensory memory (MMNm)

There were no main effects of group upon MMNm FAL in magnetometers (F=0.006, p>.93) or gradiometers (*F=1.63, p>21*). In gradiometers, MMNm responses did not differ between groups in terms of magnitude (*F=0.107, p>.74*). Whilst in magnetometers, smaller mean responses but high variability for pAD patients relative to controls for both plosive types at several ROIs (*Figure 8.5b*), resulted in a near-significant main effect of group (*F=3.44, p=.078*). Nonetheless, magnitude was significantly reduced for */t/* plosives in the pAD relative to control group at the right fronto-temporal ROI MEG122m (control-*pAD: t(21)=3.05, p=.006*), thus this measure was retained for use in further analyses.

8.2.4 Phonological processes

8.2.4.1 M50d

Unlike controls, there was no tendency for earlier M50d FAL to */d/* than */t/* plosives within the pAD group in magnetometers (*F=2.00, p>.20*), yet FAL of neither plosive significantly differed according to group (*control-pAD: /d/: t(21)=0.628, p>.53; /t/: t(21)=1.15, p>.26*). In gradiometers, the lack of a main effect of plosive (*F=0.912, p=.35*) was supported by an interaction with group (*F=12.0, p=.002*).

In terms of magnitude, like controls, the pAD group demonstrated a main effect of plosive in magnetometers (*F=30.6, p=.001*) and gradiometers (*F=17.9, p=.004*), such that difference responses were of greater magnitude to */t/* than to */d/*, *Figures 8.2a-d*. Despite a visually apparent trend in magnetometers towards a larger */t/-/d/* magnitude difference in the pAD than control group, the interaction of group with plosive only approached significance (*F=3.40, p=.079*). Compare group average time courses in *Figures 8.2a-b* with *Figures 7.2a-b*.

8.2.4.2 MMNm

Whilst the effect of plosive upon MMNm FAL in magnetometers did not vary between groups (*F=0.252, p>.62*), in gradiometers an interaction for FAL of group, plosive and hemisphere (*F=4.42, p=.050*) indicated that the latency delay observed in the control group at the left temporal ROI for MMNm to */t/* relative to */d/* plosives was not significant in the pAD group (*t(7)=1.04, p>.33*). However, despite a non-significant trend for faster MMNm to */t/* plosives in the pAD relative to control group at this ROI (*Figure 8.6a*), there were no significant group differences in FAL for either plosive (*control-pAD: /t/: t(21)=1.81, p>.08; /d/: t(10.3)=-1.53, p>*.15). Magnitude of MMNm responses did not vary according to plosive between groups in either magnetometers (*F=0.028, p>.86*) or gradiometers (*F=0.150, p>.70*).

8.2.5 Lexical/semantic processes

Unlike controls, there was no significant effect of stem upon M50d magnitude in magnetometers in the pAD group (*F(3)=0.124, p>.9*). However, given high variability, the sizeable average reduction in nonword-word magnitude difference in the pAD relative to control group (see *Figure 8.3b*) was not statistically significant at the right posterior temporal ROI MEG241m (*control-pAD: MEG241: t(8.99)=1.69, p>.12*) nor any other ROI. Nonetheless, t-tests confirmed that, unlike the control group, M50d magnitude did not differ between word and nonword contexts at any ROI within the pAD group (*Nonword-Word: all t(7)<=0.452, all p>.66*). Due to this lack of a lexicality effect in the pAD group, nonword-word magnitude difference at ROI MEG241m was retained for use in subsequent analyses.

In gradiometers, the presence of a 3-way interaction of group, stem and hemisphere (*F(3)=3.38, p=.024*) indicated a group difference in hemispheric emphasis according to stem context. In keeping with predictions, lexicality differences in magnitude at right temporal ROI MEG133g and in laterality that occurred in the control group were not found within the pAD group (*Nonwords-Words: MEG133g magnitude: t(7)=0.128, p>.9; LQ: Z(7)=-1.26, sig>.2*), see *Figure 8.4b*. Magnitude of the nonword-word difference was significantly reduced at MEG133g in the pAD relative to control group, (control-*pAD: t(21)=1.76, p=.047*). When compared directly however, the groups did not significantly differ in lateralisation of M50d responses in either word or nonword contexts (control-*pAD: both Z=-0.516, sig>.6*), nor in LQ of the nonword-word difference (*control-pAD: Z=-0.90, sig>.39*). Based on these results, nonword-word

magnitude difference both at gradiometer ROI MEG133g and at magnetometer ROI MEG241m were retained for further analyses.

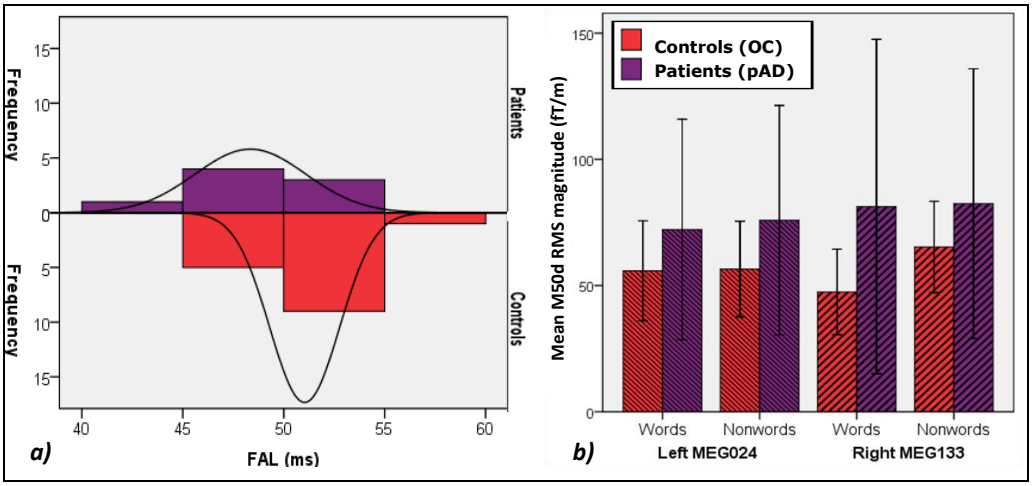


Figure 8.4: M50d in Gradiometers

a) Histogram depicts FAL for /t/ plosives according to group, pooled stems & ROIs;
b) Mean RMS magnitudes of responses for word ('play' & 'tray') versus nonword (noise & pseudoword) stem contexts, at both ROIs, for pAD and control groups. Errors bars indicate 95% confidence intervals.

8.2.6 Morpho-syntactic effects

In MMNm data in magnetometers, a 4-way interaction (*F(9)=1.95, p=.047*) reflected delayed FAL within the pAD group for */d/* relative to */t/* in the '*tray*' context, by a mean of 16.2ms (SE=4.1ms) at the left posterior temporal ROI MEG163m, whereas the difference was in the opposite direction in the control group (Mean = -16.1ms, SE=6.7ms), see *Figure 8.5a*. The group disparity in *tray /d/ - tray /t/* latency difference was on average 32.3ms (SE=7.4ms) and was highly significant (*control-pAD: MEG163m: tray /d/-tray /t/: t(21)=-4.35, p<.001*), therefore this measure was retained for further analyses.

A similar pAD group delay for /d/ relative to /t/ plosives in the '*tray*' context was not evident at gradiometer ROIs (*trade - trait: MEG024g: t(7)=0.276, p>.39; MEG133g: t(7)=-1.16, p>.28*), although a near-significant group difference at the left ROI MEG024 was in the same direction as that observed in magnetometers (*pAD-control: t(8.35)=1.65, p=.068*) .

In terms of magnitude, there were no significant group differences. Specifically, the '*played*' minus '*trade*' magnitude contrast at left gradiometer ROI MEG024g did not differ between groups (*t(21)=0.061, p>.95*). The tendency for left sided emphasis of */d/* (but not */t/*) plosives in past stem contexts seen in controls achieved only near-significance within the pAD group (*Left-Right: /d/: t(7)=1.56, p=.082; /t/: t(7)=0.714,*

p>.49), *Figure 8.6b*. LQ did not differ between groups in past stem contexts for either plosive type (*pAD-control: /d/: Z=0.129, sig>.8; /t/: Z=0.323, sig>.7*).

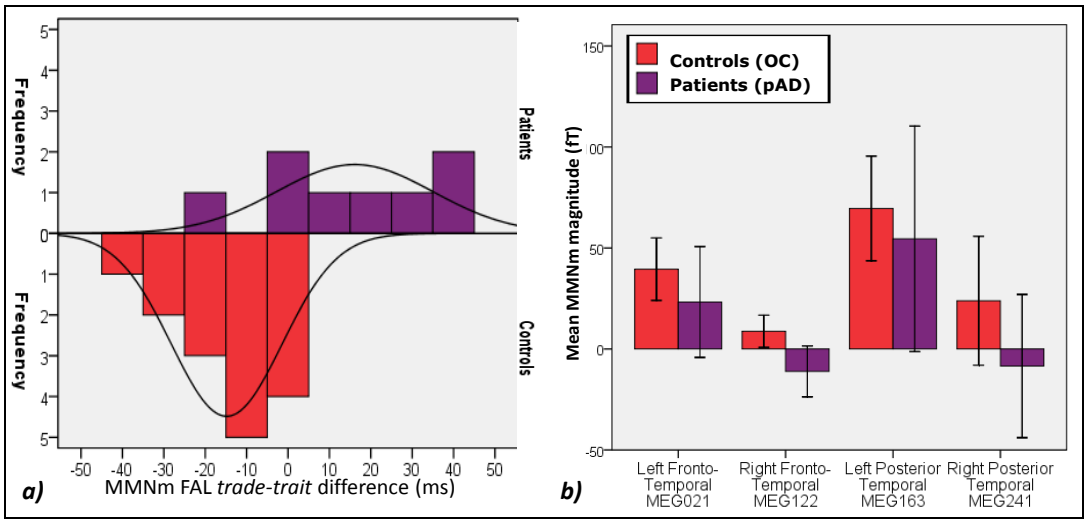


Figure 8.5: MMNm in Magnetometers

a) Histogram depicts difference in MMNm FAL for /d/ - /t/ plosives in the 'tray' stem context according to group, at MEG163m; b) Mean MMNm magnitude at each ROI pooled across stems and plosives, for pAD patients and controls. Error bars indicate 95% confidence intervals.

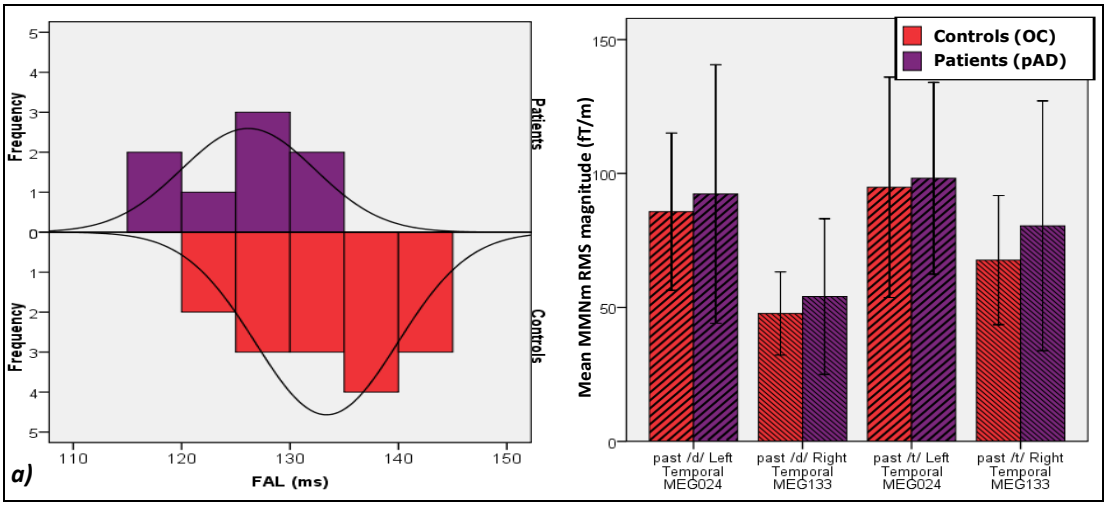


Figure 8.6: MMNm in gradiometers

a) FAL difference for /t/ plosives according to group at left gradiometer MEG024g, pooled across stems; b) Mean MMNm RMS magnitude at left and right ROIs according to plosive type within 'past' stem contexts. Error bars indicate 95% confidence intervals.

8.2.4. 10th percentile cut-offs

Table 8.1 lists the 10th percentile cut-off thresholds for measures that significantly differed between groups and their sensitivity to the diagnosis of probable dementia. Maximum sensitivity of a single measure was 87.5%, for MMNm FAL difference of 'trade' – 'trait'. Two FAL and three magnitude measures conferred sensitivity to pAD

(determined via 10th percentile threshold) at or above 50% (highlighted in *Table 8.1*). From these a total number of 'abnormal' measures for each of the main M50d, main MMNm and combined lexical/morpho-syntactic effects was computed for each individual.

Table 8.1: MEG effects differing between probable AD cases and controls
Cut-off threshold is 10th/90th percentile within age-matched control group.
Measures with sensitivity equal to or greater than 50% are highlighted.

Measure	ROIs	10th percentile cut off (normal)	Sensitivity
FAL M50d All conditions (M50d_FALg)	Pooled gradiometers MEG024g & MEG133g	>48.6ms	50.0% (4/8)
Magnitude M50d All conditions (M50d_021m)	Left fronto-temporal MEG021m	<66.0fT	50.0% (3/8)
Magnitude M50d All conditions (M50d_163m)	Left posterior temporal MEG163m	<144.6fT	12.5% (1/8)
Magnitude M50d Nonwords–Words (NW_241m)	Right posterior temporal MEG241m	>-3.3fT	50.0% (4/8)
Magnitude M50d Nonwords–Words (NW_133g)	Right temporal MEG133g	>-11.6fT/m	25.0% (2/8)
FAL MMNm *Tray /d/ - tray /t/* (TrayDT_163m)	Left posterior temporal MEG163m	<1.2ms	87.5% (7/8)
Magnitude MMNm */t/* plosives (MMN_T122m)	Right fronto-temporal MEG122m	>-11.0fT	50.0% (4/8)

With the requirement for 'normality' of no abnormal measures, the combination of M50d magnitude (M50d_021m) and latency (M50d_FALg), pooled across all conditions, conferred 62.5% sensitivity and 80.0% specificity. Magnitude of MMNm to */t/* plosives (MMN_T122m) as shown above gave 50% sensitivity and 93.3% specificity. The addition of M50d nonword-word magnitude difference (NW_241m) to MMNm *trade-trait* FAL difference (TrayDT_163m) added no further information to its already impressive classification accuracy (87.5% sensitivity and 93.3% specificity); only one individual had (borderline) 'abnormal' NW_241m with 'normal' TrayDT_163m (bottom left quadrant in *Figure 8.7a*). The combination of all 5 of the above measures gave 87.5%

sensitivity and 100% specificity with the requirement that to be classified as normal an individual must have no more than one abnormal measure. See *Figure 8.7b*.

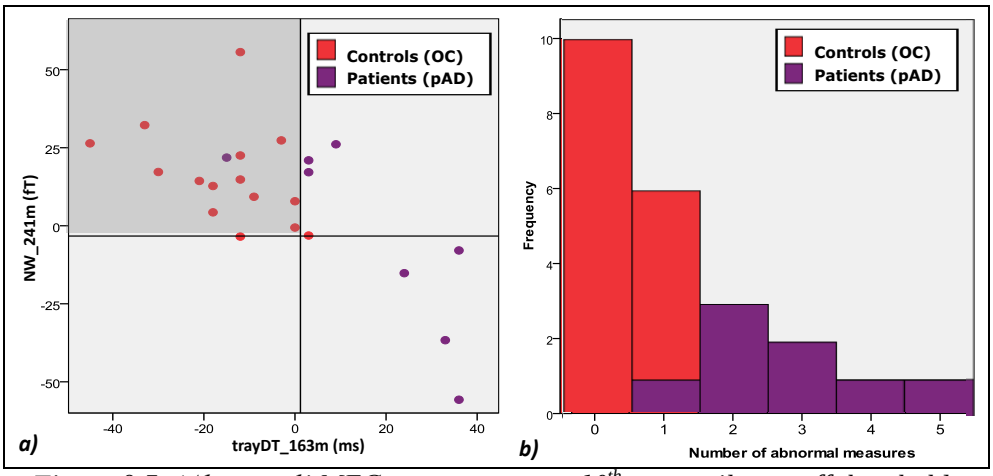


Figure 8.7: 'Abnormal' MEG measures using 10th percentile cut-off thresholds
a) Classification plot for pAD diagnosis combining M50d nonword-word context magnitude difference (NW_241m) and trade-trait MMNm FAL difference (TrayDT_163m). Reference lines = 10th percentile cut-offs, shaded area='normal' classification; b) Histogram depicts number of abnormal measures according to group.

8.2.5 Logistic Regression

8.2.5.1 Sensory gating

Three main M50d measures revealed significant group differences (*Table 8.1)*: the pAD group relative to controls had demonstrated increased magnitude at two magnetometer ROIs (M50d_021m and M50d_163m) and earlier M50d latency pooled across gradiometer ROIs (M50d_FALg). When compared against a baseline model, only the latency predictor variable, M50d_FALg, was retained in the model (*2LL=22.3, p=.006*), which had an effect size of .382 and predicted pAD group membership with 50% sensitivity and 93.3% specificity. See *Table 8.2*.

8.2.5.2 Sensory memory

One measure reflected reduction in MMNm magnitude in the pAD relative to control group, which only attained significance in response to */t/* plosive endings (MMNm_T122m, *Table 8.1*). This was retained as a predictor variable in a sensory memory model (*-2LL=20.8, p=.003*) with effect size of .443, that conferred sensitivity of 62.5% and specificity of 80.0% (*Table 8.2*). Notably, there were 7 individuals (30.4%) with predicted probabilities that ranged between 40% and 60% and the overall accuracy was lower than that obtained using the 10th percentile cut-off.

8.2.5.3 Lexico-semantic effects

Two right hemisphere ROIs for M50d nonword-word magnitude difference (NW_241m and NW_133g) were entered as predictor variables to create a model based upon lexico-semantic effects. Only NW_241m was retained in the model (*-2LL=25.7, p=.044*) with an effect size of .222, demonstrating 100% specificity but only 50% sensitivity to pAD (*Table 8.2*).

8.2.5.4 Morpho-syntactic effects

A single measure, MMNm FAL difference for the '*trade*' minus the '*trait*' condition (trayDT_163m) was entered and retained as a predictor variable in a morpho-syntactic model (*-2LL=15.5, p<.001*) that had effect size of .667 and provided sensitivity of 87.5% and specificity of 93.3% (*Table 8.2*).

Table 8.2: MEG predictors of pAD/control group membership for individual models

Effect of interest modelled	Predictor	Beta (SE)	Change in -2LL	Significance
'Sensory gating'	M50d_FALg	-1.114 (0.528)	7.47	.006
	Constant	-1.392 (0.642)		.030
'Sensory memory'	MMNm_T122m	-1.75 (0.865)	8.91	.003
	Constant	-1.85 (0.901)		.040
'Lexico-semantic'	NW_241m	-0.687 (0.402)	4.04	.044
	Constant	-0.999 (0.528)		.059
***** 'Morpho-syntactic'	trayDT_163m	2.09 (1.00)	15.2	<.001
	Constant	1.91 (1.38)		.168

** Morpho-syntactic model: $\chi^2(1)=15.2$, p<.001; $R^2_N=.667$; Overall accuracy=91.3%*

8.2.5.5 Combined MEG effects

Predictors retained in the effect of interest models were combined in a backwards step-wise LR procedure which retained 3 significant predictor variables, M50d FAL (M50d_FALg), MMNm magnitude for */t/* plosives (MMN_T122m) and *trade-trait* MMNm FAL difference (trayDT_163m). This model however reached perfect separation (100% accuracy), therefore a unique solution could not be reached. Instead, main M50d and MMNm predictors were combined, to produce a 'sensory effects' model, whilst

lexico-semantic and morpho-syntactic predictors were combined in a separate 'linguistic' model.

The sensory effects model retained M50d latency (M50d_FALg) and MMNm magnitude (MMN_T122m) (*-2LL=15.2, p=.001*), with an effect size of .646 and satisfactory goodness of fit (χ^2*=5.62, p=.69*). Accuracy was 87.0% (sensitivity=75.0%, specificity=93.3%). Regression coefficients were both negative (*Table 8.3*), indicating that likelihood of pAD increased with smaller MMNm magnitude to */t/* plosives and earlier M50d latency. The magnitude of influence of each standardised, therefore directly comparable, predictor was similar, indicating that no single predictor dominated the model. There was no evidence for multicollinearity within the model, with tolerance at 0.977 and variance inflation factor (VIF) at 1.02. The three cases misclassified (two patients and one control) had larger residuals than the others but were not outliers (Z=2.48, Z=1.82 and Z=-1.90). All Cook's values were below 1, suggesting no individual had undue influence on the final solution.

Table 8.3: Predictors of pAD group membership in 'sensory effects' LR model

Predictor	Beta (SE)	Change in -2LL	Significance
M50d_FALg	-1.08 (0.584)	5.65	.017
MMN_T122m	-1.67 (0.918)	7.09	.008
Constant	-2.45 (1.07)		.021

** Model $\chi^2(2)=14.6$, p=.001; $R^2_N=.646$; Overall accuracy=87.0%*

When trayDT_163m was entered alongside lexico-semantic predictors, only the former predictor variable was retained as significant. Thus the 'linguistic' model was identical to the 'morpho-syntactic' model detailed in *Table 8.2*. Effect size was .667 and goodness-of-fit was satisfactory ($\chi^2(8)=5.39$, *p>.71*). The regression coefficient was positive, indicating that probability of pAD increased as MMNm to '*trade*' became more delayed relative to MMNm to '*trait*'. Of the two misclassified cases, one patient had a very large residual (Z=3.96) showing that the model was a poor fit for this individual and the corresponding Cook's value was 1.41, suggesting that this case may have had undue influence on the solution. All other Cook's values (including that of the other misclassified case) were below 1 and standardised residuals ranged between -1.03 – 0.970.

8.3 Chapter summary

MEG responses during a passive linguistic modified oddball paradigm were contrasted between neurologically healthy older adults and patients diagnosed with pAD. Group differences were identified relating to effects of interest (aim 1) and these were used to develop metrics able to discriminate patients from controls (aim 2). As noted previously, using the same dataset to both identify MEG measures on the basis of group differences and develop/test the classification methods (logistic regression and 10^{th} percentile thresholds) biases these methods towards above chance performance. However, the unbiased test of these metrics will be their application to the larger memory clinic patient group in the following chapter.

8.3.1 Sensory gating

M50d magnitudes were, as predicted, greater in patients than controls, although significantly so only in magnetometers; whereas latencies were significantly earlier in patients than controls in gradiometers only (Aim 1). Of 3 ROIs retained for further analyses, two had sensitivity of 50% using 10^{th} percentile thresholding: magnitude at MEG021m and latency pooled across gradiometer ROIs (M50d_FALg). LR analysis kept only M50d_FALg as a significant predictor variable of pAD group membership (Aim 2).

8.3.2 Sensory memory

A pattern of reduced MMNm magnitude in the pAD relative to control group was evident in magnetometers, but significant only for responses to */t/* plosives (Aim 1). One measure, MMN_T122m, was retained for further analyses and demonstrated 50% sensitivity to pAD using a 10^{th} percentile cut-off threshold. The logistic regression method increased sensitivity but reduced overall accuracy. Around a third of individuals had predicted probability of pAD near to the classification threshold of 50%, suggesting that the LR model based on this predictor alone was not particularly useful in discrimination of pAD from control groups (Aim 2).

8.3.3 Phonological/acoustic effects

As seen in controls, within the pAD group M50d latency was shorter and magnitude greater for */t/* than */d/* plosives. A tendency for the magnitude effect to be enhanced in patients relative to controls did not reach significance (Aim1). The same tendencies were observed for the MMNm in controls, but not replicated in the pAD group; however there

was no evidence for significant plosive-mediated difference in MMNm between the two groups (Aim 1).

8.3.4 Lexical/semantic effects

The control group's M50d magnitude enhancement at right hemisphere ROIs for nonwords relative to words was not evident in the pAD group (Aim 1). Of two ROIs retained for further analyses, using 10th percentile thresholding sensitivity reached 50% only for magnetometer ROI NW_241m. This predictor was retained in the lexico-semantic LR model with the same sensitivity, but specificity increased to 100% (Aim 2).

8.3.5 Morpho-syntactic effects

The patient group demonstrated the same pattern of greater left hemispheric MMNm emphasis for */d/* compared to */t/* plosives in 'past' stem contexts as controls (although this contrast did not reach significance). Thus this measure was not explored further (Aim 1).

MMNm FAL was later for *tray-/d/* ('*trade*') compared to *tray-/t/* ('*trait*') in patients, but not controls, potentially reflecting difficulties in parsing conflicting semantic and morpho-syntactic information associated with the potentially grammatically ambiguous '*trade*' condition (Aim 1). The /d/-/t/ difference in MMNm FAL within the '*tray*' context at MEG163m was retained for further analysis and had 87.5% sensitivity / 93.3% specificity whether using a 10th percentile cut-off or logistic regression method (Aim 2).

8.3.6 Combined 10th percentile cut-off metric (Aim 2)

The count of 'abnormal' measures was computed from all measures that demonstrated sensitivity of 50% or greater to the diagnosis of dementia (*Table 8.1*). A combination of all 5 measures with the requirement for normality that no more than 1 measure be abnormal gave 87.5% sensitivity and 100% specificity.

8.3.7 Logistic regression of combined effects (Aim 2)

When all significant predictors retained in the individual effects models were combined into a single model, perfect separation resulted so no unique solution could be reached. Therefore, 2 models were derived, one 'sensory effects' model combined sensory gating and sensory memory effects, with overall accuracy of 87.0% (see *Table 8.3*). The second 'linguistic' model combined lexico-semantic and morpho-syntactic predictors but

retained only the morpho-syntactic MMNm *'trade'-'trait'* FAL difference (*Table 8.2*), with resultant accuracy of 92.3% (identical to that derived using the 10th percentile cut-off method).

Chapter 9
Passive spoken word paradigm in memory clinic patients

Chapter 8 identified sensory and linguistic MEG measures that significantly differed between patients with pAD and age-matched neurologically healthy controls, and used these measures to construct metrics able to classify those two groups. In the current chapter, we apply these metrics to a slightly reduced cohort of the MC patient group who participated in the active paradigm (reported in chapter 5). As noted previously, these patients included both MCI and WW sub-groups, but their final clinical outcome, and therefore firm diagnosis were not available at the time of writing. Therefore, in the same manner as in chapter 5, we attempted to assess the predictions arising from these metrics against the provisional classifications of an experienced consultant clinical neurologist. These data would ideally be followed up longitudinally, so that their utility in identifying those who subsequently converted to dementia can be assessed.

Aims & predictions:

Aim 1. Describe MEG measures in MC relative to pAD & control groups

As in chapter 5, to give an impression of the data distribution within the MC group as a whole, MEG measures that significantly differed between control and pAD groups were contrasted between MC patients and these other 2 groups. It was anticipated, given the pathological heterogeneity of the MC group, that group averages would fall somewhere between the 2 other groups, and that the distribution would be far broader.

Sensory gating: EEG P50 enhancement, more marked at slower presentation rates, was reported in MCI patients relative to controls, in both active and passive paradigms (Golob, et al., 2002; Irimajiri, et al., 2005), but did not demonstrate a relation to neuropsychological test scores. The amplitude increase was greater in individuals who subsequently converted from MCI to dementia (Golob, et al., 2007); notably, there was high intra-group variability in this measure. In light of these findings, we expected increased M50d amplitude in the MC group relative to controls. These previous studies (which used non-linguistic stimuli only) also reported latencies that were either delayed or not significantly different from those of controls, which is in the opposite direction to our finding of an earlier M50d latency for speech stimuli in pAD patients relative to controls. Nonetheless, given our findings in chapter 8, it was predicted that the MC group

on average would demonstrate M50d latencies intermediate to those of the control and pAD groups.

Sensory memory: Auditory MMN has not been specifically studied in a cohort of MCI patients. However, given the MMNm magnitude reduction within our pAD patients, we expected the MCI patients within our MC group to show a similar pattern, placing the group average between those for the pAD and control groups.

Lexical/semantic processes: We hypothesised that M50d nonword-word differences reflect perceived saliency differences between encountered lexical and non-lexical stimuli and are thus dependent upon lexical/lexico-semantic representations. Semantic deficits have been observed in MCI patients (Dudas, Clague, et al., 2005), but less markedly than in mild pAD (Adlam, et al., 2006; Perry, et al., 2000; Rogers & Friedman, 2008). On this basis, and the basis of the heterogeneity of the MC group, we predicted smaller discrepancies in lexicality effects between MC and control groups than those found between pAD and control groups.

Morpho-syntactic processes: We interpreted the MMNm delay for '*trade*' relative to '*trait*' in the pAD group as indicating difficulty in inhibiting conflicting linguistic processing cues from phonological and lexical information (see chapter 10 for discussion). Given that MCI patients show deficits in language abilities (Mioshi, et al., 2006), we expected the MMNm *'trade'-trait'* latency contrast to be sensitive to these language deficits and anticipated increased delay for *'trade'* relative to *'trait'* for a proportion of MC patients, resulting in a mean difference intermediate to those of control and pAD groups, with wider variance.

Aim 2. Explore relations of MEG metrics to behavioural measures

As patients with pAD show deficits upon a range of cognitive functions, just as in chapter 5 for the active paradigm, we were interested to see how neuropsychological scores related to the passive paradigm MEG measures. The larger group size and broader range of scores, overlapping with normality, in the MC group made the data most suitable for such analyses.

Sensory gating: Lack of relationship between P50 amplitude and neuropsychological tests of memory and language has been reported (Irimajiri, et al., 2005), although P50 increase was more marked in MCI patients who demonstrated impairment in multiple domains

than in those whose impairment was restricted to the memory domain (Golob, et al., 2007). On the basis of these ERP findings, it was unclear whether we were likely to detect any clear-cut relationships between behavioural performance and M50d magnitude.

Sensory memory: Greater long-term memory deficits have been shown to predict reduced MMN magnitude in clinical conditions such as schizophrenia (Baldeweg, et al., 2004), although this has not been investigated in MCI or pAD patients. Therefore we expected that MMNm magnitude might differ according to behavioural measures of memory within the MC group.

Lexical/semantic processes: Behavioural decrements in some pAD patients attributed to semantic memory impairment were reported in several studies (Adlam, et al., 2006; Davies, et al., 2008; Lambon Ralph, et al., 2001; Perry, et al., 2000). If M50d nonword-word differences are sensitive to semantic memory function, we anticipated lexicality effects to correlate positively with scores for behavioural tests that rely upon semantic memory (e.g. both recall tests, ACE-R total, plus memory, language and fluency sub-components).

Morpho-syntactic processes: If the MMNm *'trade'-'trait'* FAL difference in pAD patients is a measure of ability to inhibit interference arising from the presence of conflicting phonological and lexical information, we would expect performance upon the ACE-R language component (comprising tasks such as spelling, reading and writing) to be affected by this disruption to linguistic processing.

Aim 3. Assess utility of MEG measures in predicting clinician's opinion

To assess the accuracy of passive paradigm MEG metrics developed in chapter 8 in distinguishing MCI from WW sub-groups we examined AUC measures from ROC curves. In an attempt to gauge whether passive MEG measures added additional predictive ability to the behavioural data, we ran a backwards step-wise LR procedure and assessed if the addition of passive paradigm MEG measures to the most useful standardised behavioural variables improved model accuracy. As noted previously, individuals were classified as MCI according to the clinician's best-guess, based upon available standard clinical information, but no definitive diagnoses were available at the time of writing; the results of this stage of analyses should therefore be treated with caution.

9.1 Method

9.1.1 Participants

Twenty-eight (15 males) of the 30 individuals from the MC group who previously participated in the active memory paradigm (see chapter 5) subsequently completed the current passive paradigm. All but two were right-handed (one was left-handed, the other ambidextrous) and they ranged in age from 56 to 76 years with a mean age of 66.8 years (SD=5.5 years), age did not significantly differ between MC and control (control-*MC: t(41)=0.209, p>.83*) or pAD (MC-pAD: *t(34)=1.82, p>.07*) groups. Patients' participation in this study was approved by a local NHS regional ethics committee (LREC code: 08/H0306/68). All gave their written informed consent and were unpaid for their participation but received reimbursement of travel expenses and refreshments during their visits. Of this MC group, 7 individuals were members of the MCI sub-group and the remaining 21 comprised the WW sub-group.

9.1.2 Procedure, pre-processing and SNR

The design, stimuli and procedure were identical to those used with all other passive paradigm participants (chapters 6-8). Data were recorded and pre-processed and SNR computed in an identical manner as for the other groups.

9.1.3 Analyses

For this dataset, only MEG measures identified as significantly differing between the control and pAD groups in the previous chapter were examined. Magnitude, FAL and LQ were computed in a manner identical to that used in previous chapters.

9.1.3.1 MEG measures in MC relative to other groups

Pair-wise comparisons of magnitude and FAL were made between the MC and other groups via independent t-tests, or non-parametric tests (Wilcoxon signed ranks or Mann-Whitney U-test) where appropriate. One-tailed tests were used, as all values were expected to be intermediate to those of the other 2 groups. Additionally, for group comparisons of lexico-semantic and morpho-syntactic effects, 2-way ANOVAs were used to assess interactions of group with size of M50d lexicality effect and difference in MMNm FAL for *trade* versus *trait*, respectively.

9.1.3.2 Examination of relationships between MEG metrics and behaviour

Within the MC group, correlation coefficients were computed between each behavioural measure (ACE-R total and sub-component scores and cued/free recall of items following the active MEG task) and the MEG measures identified in chapter 8 as sensitive to dementia. Spearman correlations were used for comparisons that involved the MEG 10^{th} percentile metric (due to the ordinal nature of the data), ACE-R attention/orientation and visuo-spatial sub-components (due to limited range within these measures); Pearson correlation coefficients were calculated for all others. Correction for multiple comparisons was applied to account for the ACE-R total being comprised of the sum of the other ACE-R metrics, such that the alpha value was divided by a factor of 2 for each ACE-R measure, the same adjustment was applied for comparisons involving cued and free recall of active MEG task items. Additional correction was made to account for the 10^{th} percentile metric and LR metrics being comprised of the individual effects of interest being examined, such that alpha value was further divided by the number of times an effect of interest was included either individually or incorporated as part of a metric.

9.1.3.3 Sensitivity of MEG and behavioural measures to clinician's opinion

With the clinician's opinion as the state variable, ROC curves were constructed for behavioural and MEG measures, deviation of AUC (area under the curve, see *section 5.1.3.4*) from 0.5 was used to establish whether each measure was accurate above chance level in classifying MCI and WW sub-groups.

9.1.3.4 Combined MEG/neuropsychology LR model for clinician's opinion

Logistic regression analysis with clinician's diagnosis (MCI or WW) used as the dependent categorical variable was performed against the baseline model in a similar manner as for the control/pAD LR model in chapter 4. In this case, all ROIs that significantly differed between control and pAD or MC groups were incorporated as MEG predictor variables. A separate backwards step-wise analysis was performed against the baseline model with the neuropsychological scores as predictors, such that predictors that increased the -2LL by a significance level of less than 0.1 were removed from the model. In the final step, the retained MEG predictor variables were added, again using a backwards step-wise procedure, to the ACE-R model and their impact upon the 'ACE-R only' model-fit assessed.

9.2 Results

9.2.1 SNR

Of the 28 memory clinic patients who completed this paradigm, one was excluded due to low SNR (below 1.5) for multiple blocks in both sensor types whilst another had unusable data due to a head-localisation software error. This left 26 participants whose data were suitable for analysis.

As in the control group, SNR in magnetometers was significantly higher than in gradiometers (*Magnetometers-Gradiometers: Z=4.16, sig<.001*). SNR pooled across blocks did not significantly differ between control and MC (control-*MC: Magnetometers: Z=-1.50, sig=.14; Gradiometers: Z=-1.94, sig>.05*), or MC and pAD groups (*MC-pAD: Magnetometers: Z=-0.714, sig>.47; Gradiometers: Z=-0.084, sig>.93*).

9.2.2 MEG measures in MC patients

MC group average time courses and topographies for */d/* and */t/* plosives, pooled across contexts are presented for both sensor types in *Figure 9.1*. The average tendencies for both magnitude and latency appeared intermediate between the control (*Figure 7.2*) and pAD (*Figure 8.2*) group averages.

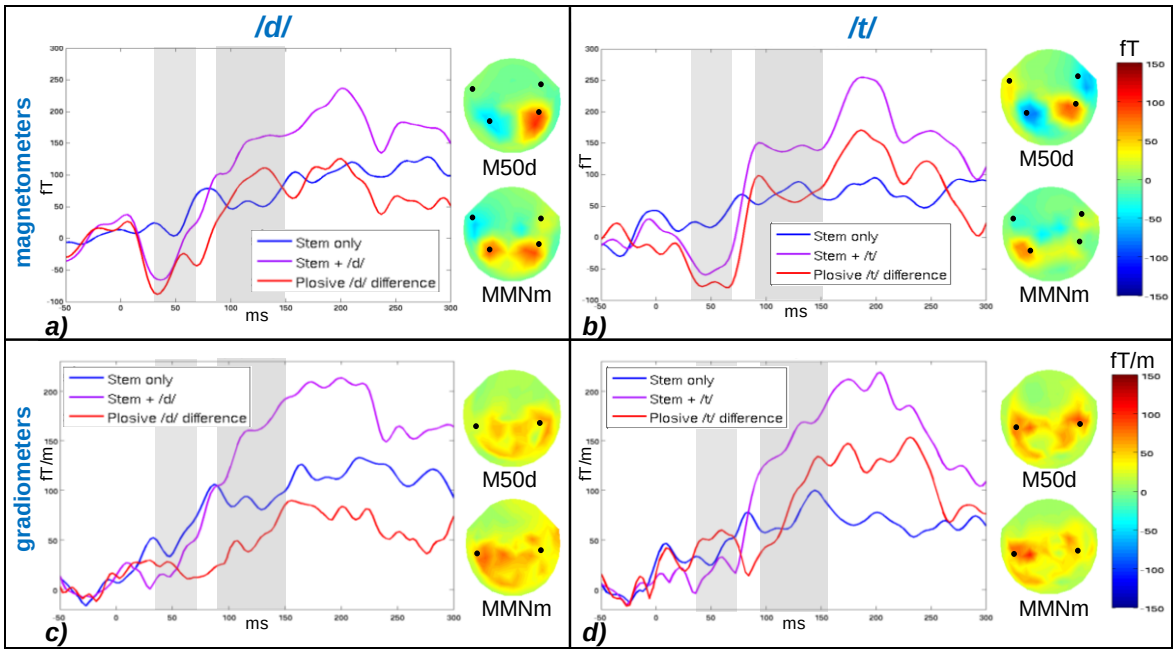


Figure 9.1: MC group mean difference responses to plosives, pooled across stem contexts
a) /d/ plosive in magnetometers; b) /t/ plosive in magnetometers;
c) /d/ plosive in gradiometers; d) /t/ plosive in gradiometers.
Within each box: Left: Group mean time course from -50-300ms at maximal ROI, shaded areas indicate time windows of interest (Magnetometers = left posterior temporal MEG163m; Gradiometers RMS of difference = left temporal MEG024g); Right: Group average topographies across M50d (35-65ms) & MMNm (90-150ms) windows, black circles indicate ROIs.

9.2.2.1 Sensory gating effects

M50d FAL at pooled gradiometer ROIs was significantly later in the MC relative to pAD group by a mean of 2.3ms (SE=1.0ms) but did not significantly differ between MC and control groups (M50d_FALg: control-MC: t(39)=0.525, p>.30; MC-pAD: t(32)=2.38, p=.012), *Figure 9.2a*.

M50d magnitudes were significantly lower in MC than pAD groups at both left hemisphere magnetometer ROIs, but did not significantly differ between MC and control groups (*MEG021m: control-MC: t(39)=0.007, p>.99; MC-pAD: t(32)=-1.89, p=.034; MEG163m: control-MC: t(39)=-0.476, p>.32; MC-pAD: t(32)=-2.03, p=.026*), *Figure 9.2b*.

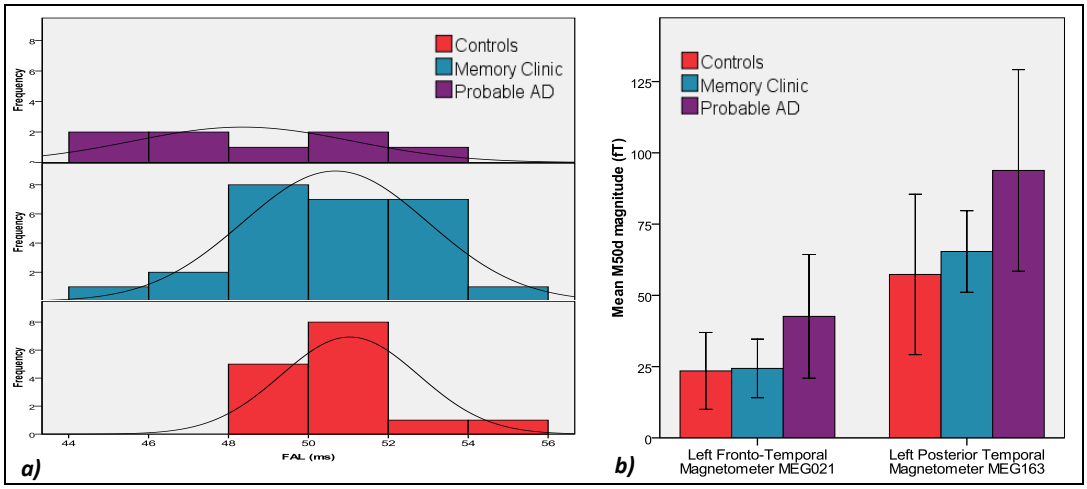


Figure 9.2: Main M50d effects in memory clinic patients

a) Histogram depicts M50d FAL at pooled gradiometer ROIs; b) Mean M50d magnitudes at left hemisphere magnetometer ROIs. Error bars indicate 95% confidence intervals.

9.2.2.2 Sensory memory effects

The pattern of MMNm magnitude for */t/* plosives was clearly in the expected direction (*Figure 9.3*). Magnitude was greater in the MC relative to pAD group *(MC-pAD: t(18.8)=1.98, p=.032)*, but the decrement in the MC relative to control group was not statistically significant (*control-MC: t(38.4)=-1.05, p>.17*).

9.2.2.3 Lexical / Semantic effects

Although the pattern of interaction of lexicality with group for M50d magnitude was similar in both sensor types (*Figures 9.4a-b*), it was significant at the right hemisphere gradiometer ROI MEG133g (*F(2)=4.61, p=.015*) but not magnetometer ROI MEG241m (*F(2)=1.41, p>.25*). The M50d nonword-word magnitude difference at the gradiometer ROI (NW_133g) was significantly reduced for the MC relative to control group, but not

for the pAD relative to MC group (*control-MC: t(39)=3.02, p=.002; MC-pAD: t(32)=-0.770, p>.44*), *Figure 9.4b*. The lack of significant interaction at the magnetometer ROI was likely due to the presence of 2 outliers (>2.5SD from the group mean) in the MC group, see *Figure 9.4c*.

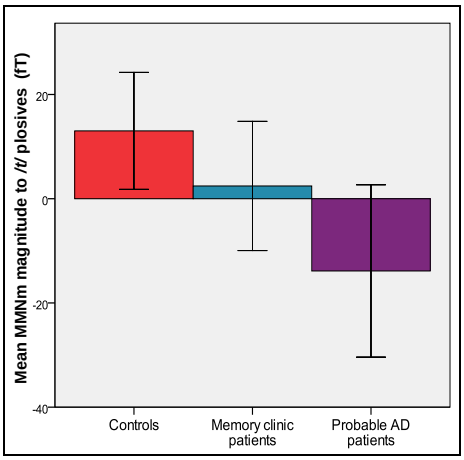


Figure 9.3: Main MMNm effect in MC patients
MMNm magnitude to /t/ plosives at right fronto-temporal magnetometer MEG122m. Error bars indicate 95% confidence intervals.

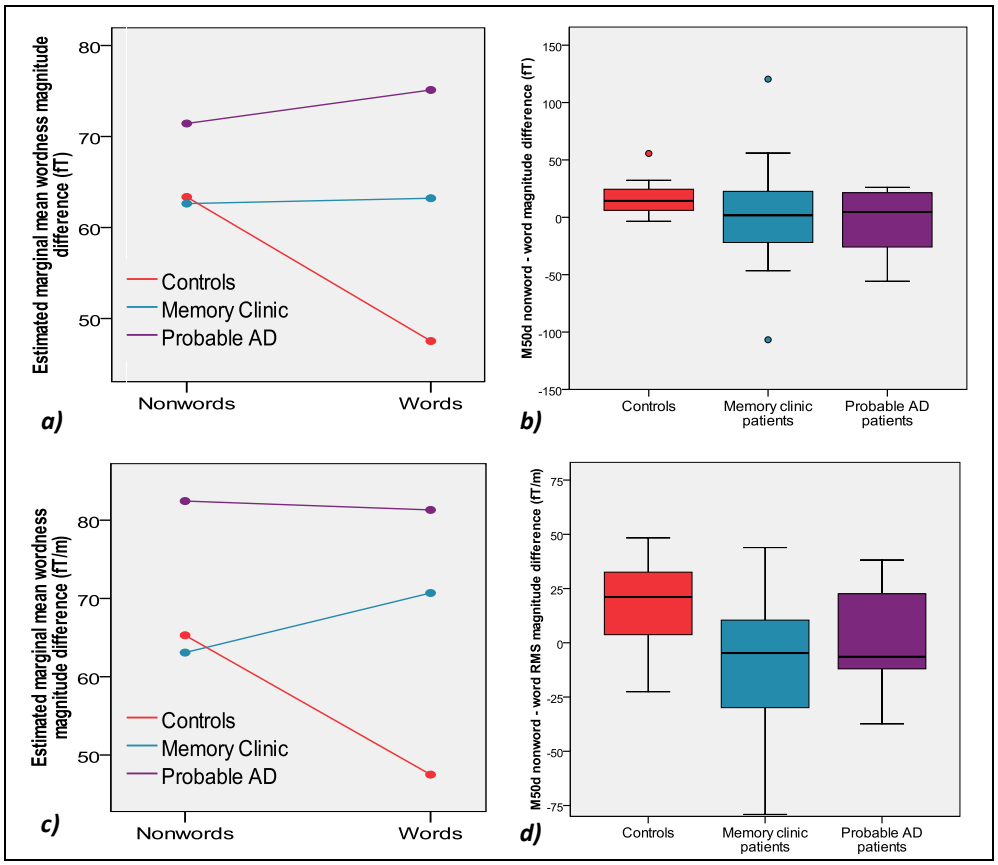


Figure 9.4: Lexical/semantic M50d measures in MC patients
a) & c) M50d magnitude interaction plots for group and lexicality at right-sided ROIs; b) & d) Boxplots of M50d nonword – word magnitude difference at right-sided ROIs; a)&b) Magnetometer MEG241m; c)&d) Gradiometer MEG133g.

9.2.2.4 Morpho-syntactic effects

MMNm FAL demonstrated an interaction of group with plosive within the '*tray'* context at magnetometer MEG163m (*F(2)=6.14, p=.004*). Whilst *'trait'* MMNm latency was longer than that for *'trade'* in controls, FAL of the conditions did not significantly differ in the MC group as a whole, and MMNm for '*trade'* was delayed relative to that for *'trait'* in the pAD group (*Figure 9.5a*). MMNm latency difference for *'trade'* minus *'trait'* conditions (trayDT_163m) was greater in the MC relative to control group and greater still in the pAD group(*control-MC: t(39)=-2.11, p=.021; MC-pAD: t(32)=-2.06, p=.024*). As evident in *Figure 9.5b*, the MC group distribution broadly overlapped with those of both the pAD and control groups.

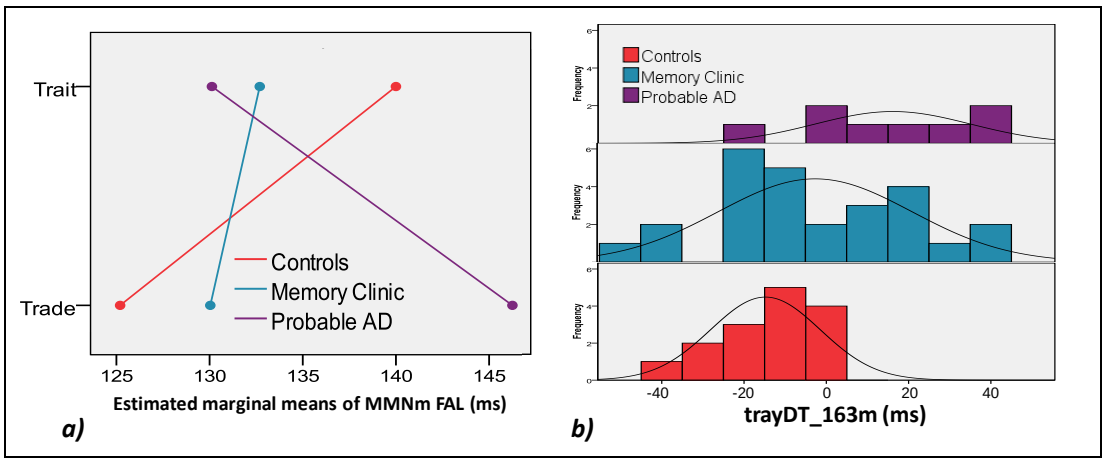


Figure 9.5: Morpho-syntactic MEG effect in MC patients
a) MMNm FAL interaction plot of plosive x group in the 'tray' context at MEG163m;
b) MMNm FAL 'trade' minus 'trait' difference, according to group at MEG163m.

9.2.3 Comparisons of behavioural tests and passive paradigm MEG metrics

Correlations within the MC group of all behavioural measures with the MEG 10th percentile metrics and LR models defined in the last chapter are listed in *Table 9.1*. Scatter plots of significant and near-significant relationships are shown in *Figures 9.6a-h*, data points from control and pAD groups are included and those within the MC group are colour-coded according to clinician's provisional diagnosis.

Neither sensory gating (M50d latency and magnitude) nor sensory memory (MMNm magnitude to */t/* plosives) measures bore significant relationships with behavioural scores within the MC group. The sensory effects LR model, which combined measures of sensory gating and magnitude, also showed no relationship to performance on the higher cognitive functions assessed by the behavioural tests employed here.

M50d nonword-word magnitude difference at magnetometer ROI MEG241m correlated positively with ACE-R verbal fluency (*Figure 9.6h*), although this did not

survive correction for multiple comparisons. A non-significant trend for correlation with free recall performance is illustrated in *Figure 9.6a*. There was no clear clustering of WW/MCI sub-groups in either of these relationships and indeed there appeared to be a tendency for more extreme measures within those classified by the clinician as WW.

Table 9.1: Correlations between MEG and behavioural measures in MC group

		Cued Recall (N=26)	Free Recall (N=25)	ACE-R Total (N=26)	ACE-R Memory (N=26)	ACE-R Vis-Spat (N=26) #	ACE-R Attention (N=26) #	ACE-R Fluency (N=26)	ACE-R Language (N=26)
Combined 10th percentile metric # **	r	-.393	-.567	-.450	-.405	.085	-.211	-.119	-.413
	p	.023	.002	.011	.020	.680	.151	.151	.018
M50d magnitude M50d_021m **	r	-.034	-.039	.015	-.143	.069	-.181	.169	.333
	p	.435	.426	.924	.243	.738	.188	.408	.096
M50d latency M50d_FALg **	r	-.111	.046	-.057	-.178	.193	-.125	.199	-.196
	p	.590	.413	.780	.384	.173	.542	.165	.383
MMNm magnitude MMNm_122m **	r	.099	.191	-.063	.044	-.317	.038	-.177	.157
	p	.316	.180	.758	.416	.114	.427	.388	.222
Lexico-semantic NW_241m *	r	.104	.313	.289	.192	-.090	.077	.338	.247
	p	.307	.064	.076	.174	.662	.354	.045	.112
MEG LR sensory effects model **	r	.034	-.231	.187	.201	.298	.068	-.008	.043
	p	.868	.133	.360	.324	.140	.640	.485	.834
MEG LR morpho-syntactic model *	r	-.234	-.281	-.202	-.225	.379	-.170	.044	-.354
	p	.125	.087	.161	.135	.056	.203	.832	.038

Corrected alpha levels: * = .05/4 = 0.0125, ** = 0.5/6 = .008

Blue shading = correlation significant at corrected alpha level (one-tailed);

grey shading = correlation significant at p=.05 level, uncorrected.

Spearman's correlation coefficient was used for comparisons involving 10th percentile metrics, ACE-R attention/orientation and visuo-spatial sub-components.

The morpho-syntactic LR model which included only the MMNm FAL *trade – trait* difference predictor variable correlated negatively with ACE-R language score, although this did not survive the conservative Bonferroni correction we applied. There was little evidence for clustering according to MCI/WW sub-groups, see *Figure 9.6f.*

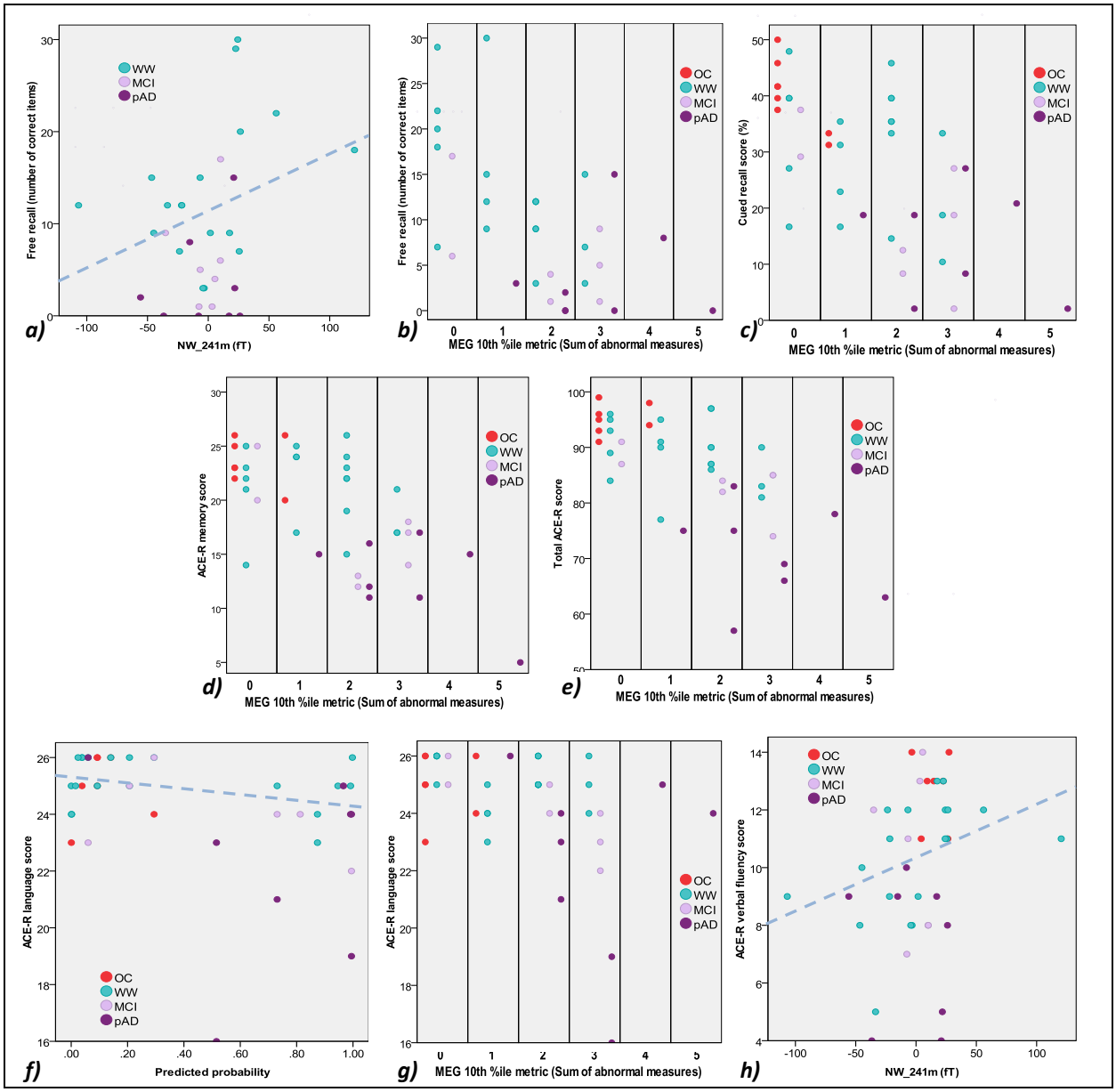


Figure 9.6: Relationships of passive MEG metrics with behavioural performance

a) M50d nonword-word magnitude difference at MEG241m with free recall; b)-e) Combined MEG 10th percentile metric with free recall, cued recall, ACE-R memory and total ACE-R score respectively; f) Probability of dementia from morpho-syntax LR model with ACE-R language; g) Combined MEG metric with ACE-R language; h) M50d nonword-word magnitude difference at MEG241m with ACE-R verbal fluency. Fit-lines indicate correlations within the MC group only.

The combined MEG 10th percentile metric exhibited negative correlations with several behavioural measures, indicating that fewer 'abnormal' MEG measures within an individual was associated with better behavioural performance. The most prominent relationship was with free recall of task items subsequent to the active MEG session (*Figure 9.6b*), which survived correction for multiple comparisons. Additional

relationships were present with ACE-R total score (*Figure 9.6e*), cued recall score (*Figure 9.6c*) and ACE-R memory and language sub-components (*Figures 9.6d&g*), but did not survive Bonferroni correction. There was some separation upon this 10th percentile metric evident for 5 out of 7 MCI-classified cases who had 2 or more abnormal measures and clustered especially upon the relationships with mnemonic measures (ACE-R memory, cued and free recall), *Figures 9.6b-d*. Some WW cases were also incorporated into these clusters.

9.2.4 Agreement of behavioural and MEG measures with clinician's opinion

Table 9.2 lists the AUC and significance for behavioural measures and MEG metrics, along with optimal thresholds for discriminating MCI and WW cases, and sensitivity and specificity. For the behavioural measures, total ACE-R score, cued recall and free recall remained significant predictors of the clinician's provisional MCI classification in this 26 case MC cohort: as evident from *Figure 9.9*, free recall was the most accurate predictor of MCI classification. ACE-R memory score *became* a significant predictor in this smaller cohort, whilst the language sub-component was not able to predict MCI classification significantly above chance.

None of the MEG metrics predicted the clinician's 'best-guess' diagnosis significantly above chance (see *Figure 9.7*). The morpho-syntax LR model came marginally close to significance (p<.1, c.f. bottom row) and adjustment of the classification cut-off to 21% produced the same accuracy as that of the total ACE-R (using the standard cut-off of 88), correctly identifying 6 out of 7 MCI-classified cases, but misclassifying 36.8% of WW cases.

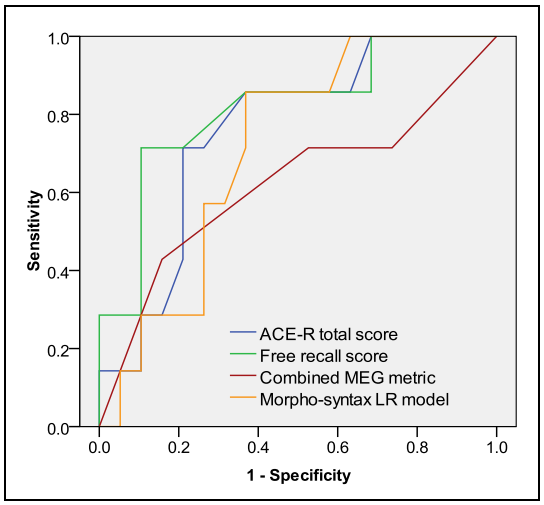


Figure 9.7: ROC curves for clinician's MCI classification

Table 9.2: Ability of measures to classify WW and MCI sub-groups

Measure	AUC (SE)	Sig.	Optimal MCI/WW threshold (Control threshold)	Sensitivity (using control cut-off)	Specificity (using control cut-off)
Cued Recall	.763 (.105)	.043	30.2% (31.3%)	85.7%	57.9%
Free Recall	.806 (.104)	.020	6 (-)	91.4%	77.8%
ACE-R total	.759 (.101)	.046	88 (91)	85.7%	63.2%
ACE-R Memory	.759 (.121)	.046	20 (22)	85.7%	42.1%
ACE-R Visuo-Spatial	.511 (.127)	.931	15 (15)	57.1%	52.6%
ACE-R Attention/Orientation	.635 (.128)	.298	17 (17)	57.1%	68.4%
ACE-R Verbal Fluency	.492 (.152)	.954	8 (10)	42.9%	57.9%
ACE-R Language	.733 (.117)	.073	24 (24)	57.1%	78.9%
Sensory gating MEG metric	.459 (.132)	.751	1 (0)	14.3% (14.3%)	100% (73.7%)
Sensory memory MEG metric	.602 (.128)	.435	0 (0)	57.1%	63.2%
Lexical/morpho-syntactic MEG metric	.586 (.134)	.506	0 (0)	71.4%	36.8%
Combined MEG metric	.620 (.139)	.355	2 (1)	71.4% (71.4%)	47.4% (26.3%)
Sensory effects MEG LR model	.338 (.113)	.214	18% (50%)	42.9% (14.3%)	47.4% (68.4%)
Morpho-syntax MEG LR model	.714 (.102)	.099	20.7% (50%)	85.7% (57.1%)	63.2% (68.4%)

** Blue shading = ability to discriminate sub-groups significantly above chance*

9.2.5 Logistic regression model for clinician's classification of MC patients

9.2.5.1 Neuropsychology-only model

As was the case with the slightly larger cohort included in the active paradigm analysis (chapter 5), when all ACE-R measures were entered as predictor variables for MCI classification in a backwards step-wise logistic regression procedure, only ACE-R total score was retained in the model. The resultant model (*-2LL=25.7, p=.032*) had an effect size of .236 but rather low accuracy at 69.2%, with 89.5% specificity but only 14.3% (1/7) sensitivity to the clinician's classification of high likelihood MCI.

Table 9.3: Significant neuropsychological predictors for MCI classification

Predictor (Abbreviation)	Beta (SE)	Change in -2LL	Significance
ACE-R total (At)	-0.507 (0.269)	-4.61	.032
Constant	-2.56 (1.03)		.013

**Model $\chi^2(1)=4.61$, $p=.03$; $R^2_N=.236$, Overall accuracy=69.2%*

9.2.5.2 Addition of MEG predictors to neuropsychology-only model

With clinician's opinion as the dependent outcome variable, none of the individual MEG predictor variables were retained when compared against a baseline model. Adding the morpho-syntactic predictor variable, trayDT_163m, to the neuropsychology-only model increased accuracy to 76.9% with equivalent specificity of 89.5% and higher sensitivity at 42.9% (3/7) and model effect size of .339; however, this change did not reach statistical significance ($\chi^2(1)=2.31$, $p>.12$).

Adding sensory gating predictors M50d_021m and M50d_FALg to the neuropsychology-only model increased accuracy to 80.8%, with higher specificity at 94.7% and sensitivity at 42.9% and model effect size of .260, however, this change was also not statistically significant ($\chi^2(2)=0.507$, $p>.77$).

9.3 Chapter summary

This chapter sought to test the application of the passive MEG paradigm in distinguishing between memory clinic (MC) patients classified as MCI or WW by an experienced consultant neurologist. A caveat was that we had only provisional diagnoses for the MC patients and ideally would like to follow these up longitudinally to assess whether any identified MEG measures were sensitive to incipient dementia (i.e. those individuals who subsequently develop dementia proper). Basic differences in the MC relative to other groups were established for effects of interest shown to differ at spatio-temporal ROIs between pAD patients and age-matched controls in chapter 8. We went on to identify how metrics derived from each effect related to behavioural scores. Finally using ROC and logistic regression analyses we assessed whether MEG metrics developed in chapter 8 were able to differentiate between MCI and WW subgroups and to identify which (if any)

individual MEG measures were able to classify these sub-groups more accurately than neuropsychological data alone. Findings are summarised below:

9.3.1 MEG findings in MC group (Aim 1)

The expected broad variability in MEG measures showed a high degree of overlap with both control and pAD groups. As predicted, the MC group averages generally fell into an intermediate position between those of the other 2 groups.

9.3.1.1 Sensory gating effects

M50d latency (M50d_FALg) was earlier and magnitude (M50d_021m and M50d_163m) greater in the MC than control group, but less so than in the pAD group. Significant differences were evident between MC and pAD but not control groups.

9.3.1.2 Sensory memory effect

MMNm magnitude to */t/* plosives at MEG122m conformed to the expected pattern of control>MC>pAD. It was significantly greater for MC relative to pAD pastients, but its reduction in the MC relative to control group was not statistically significant.

9.1.3.3 Lexical/semantic effects

The M50d magnitude advantage of nonwords over words at right hemisphere ROIs was, as in the pAD group, diminished in the MC group relative to controls; this however only reached significance at the gradiometer ROI MEG133g. No significant group differences were identified between MC and pAD patients.

9.1.3.4 Morpho-syntactic effect

In the MC group, difference in MMNm FAL difference for *'trade*' minus *'trait'* responses was significantly greater than in the control group and less than in the pAD group. The broad MC distribution overlapped with both groups.

9.3.2 Correlations between MEG and behavioural measures (Aim 2)

Neither sensory gating nor sensory memory measures, nor the sensory effects LR model which combined them, related significantly to any behavioural measures considered here. It is possible that altered sensory processes reflected in these measures may not have

impacted noticeably upon the higher cognitive functions assessed by the behavioural tests employed.

The relationship between M50d nonword-word magnitude difference and ACE-R verbal fluency implied that there was more ready access to contents of semantic memory in those whose automatic right hemisphere brain responses showed greater enhancement for items without (compared to those with) existing lexical representations. A questionable relationship with free recall was also noted.

A negative correlation of predicted probability of dementia from the morpho-syntactic LR model with ACE-R language score indicated better performance of language tasks such as comprehension, spelling and writing in those individuals who exhibited a smaller degree of disruption of speech processing by conflicting phonological/lexical signals.

The combined MEG 10^{th} percentile metric, although derived only from the above measures exhibited relationships to neuropshychological tests, not evident from its individual contributory parts. Relationships with memory measures in particular demonstrated clustering of MCI cases with low memory performance and multiple 'abnormal' MEG measures, although these clusters did not include exclusively MCI-classified cases. Relationships with total ACE-R score and language sub-component demonstrated no such obvious clustering of sub-groups.

9.3.3 Utility of MEG measures in predicting clinician's provisional diagnosis of MCI (Aim 3)

None of our MEG metrics were able to distinguish significantly above chance between those individuals provisionally diagnosed by the clinician as MCI from those he considered to be WW, although the morpho-syntactic LR model did come close to significance and at optimal cut-off threshold (predicted probability of dementia > 21%) had the same level of accuracy (69.2%) as ACE-R total score.

No MEG predictor variables were able to improve to a statistically significant extent upon the accuracy of the LR model classification based upon ACE-R scores alone. Although addition of either the morpho-syntactic predictor variable, or both M50d predictor variables to the neuropsychology-only model increased sensitivity from 14.3% (1/7) to 42.9% (3/7), given the small proportion of positive (MCI) cases these improvements in overall accuracy did not reach statistical significance.

Chapter 10
Discussion

The preceding chapters employed two MEG paradigms to identify potential biomarkers for incipient dementia, and assessed these biomarkers' ability to discriminate between memory clinic (MC) patients provisionally classified as either worried well (WW) or suffering from mild cognitive impairment (MCI). For each paradigm, we first established the presence of several effects of interest (through contrasts of various experimental conditions) and their relation to memory performance within a group of healthy young individuals. We then characterised the same effects in healthy older controls, in order to examine effects of age, and to define spatio-temporal regions of interest (ROIs) for later use in the patient groups. We went on to identify which of these effects distinguished patients with pAD from the older control group, and established several combinations of effects (MEG "metrics") that maximally distinguished individuals with versus without pAD. Finally we turned to the MC group and, in addition to contrasting their effects of interest relative to the control and pAD groups and assessing how these related to behaviour, we examined the ability of the MEG metrics to classify the provisional diagnoses of this diverse group as MCI or WW. Ultimately, we would like to assess the ability of metrics to predict which individuals in this MC group subsequently convert to dementia; however this information is not yet available at the time of writing.

10.1 Active memory paradigm in healthy young individuals

In the first experimental chapter, we tested a group of healthy young individuals on an 'active' memory paradigm believed to index aspects of semantic and episodic memory, using concurrent MEG and EEG in order to replicate previous ERP effects in this paradigm, and, for the first time, check for their MEG counterparts. Trials consisted of a spoken auditory category phrase followed by a visual word, and participants pressed one of two keys to indicate whether the word was congruent or incongruent with category. By further repeating trials, a 2x2 design was formed with factors Congruency and Repetition (Initial versus Repeat). Within this design, we focused on 3 a priori contrasts of interest (see chapter 1): between congruent and incongruent initial trials (believed to isolate semantic memory), between initial and repeat incongruent trials (believed to isolate semantic priming) and between initial and repeat congruent trials (believed to isolate episodic memory). Furthermore, we identified an additional post-hoc effect of interest – a

main effect of repetition – that occurred earlier than these 3 a priori effects. We next summarise the findings associated with each effect for the young group, before turning to their modulation by age and across patient groups.

10.1.1 N400(m) congruency effect

A reduction in EEG negativity for initial presentations of congruent relative to incongruent items from approximately 350-550ms was accompanied by a reduction in MEG magnitude during the same time window. The congruency effect was significantly right-lateralised in EEG, in keeping with previous EEG literature (Kutas & Hillyard, 1982), whilst it was left-lateralised in planar gradiometers indicating a left-hemispheric source as expected from a previous MEG study (Halgren, et al., 2002), this emphasises the more direct localising power of MEG planar gradiometers. Congruency effect magnitude was positively correlated with cued recall performance in both EEG and MEG modalities. As cued recall scores were comprised primarily of correctly recalled congruent items, it is likely that those who subsequently performed better had achieved better semantic integration (Hagoort, 2008; Kutas & Federmeier, 2000).

10.1.2 N400(m) incongruent repetition effect

EEG negativity was reduced for repeat relative to initial presentation of incongruent items, during a comparable time window to that observed for the congruency effect above. A trend for right lateralisation in EEG was less marked than for the congruency effect, which might reflect the smaller incongruent repetition effect magnitude, whilst a left-sided emphasis in MEG was again evident. Relationships between incongruent repetition effect magnitude and cued recall performance were evident for all sensor types, and coincided spatially with behavioural relationships of the congruency effect, most markedly for EEG. The similarity of behavioural relationships with both N400(m) effects is unsurprising, given that they share half of their variance (the initial incongruent condition); effects on this condition that relate to subsequent memory would be evident in correlations with behaviour for both congruency effect and incongruent repetition effect. Although the repetition effect was emphasised for incongruent items, where the N400(m) component was most prominent, the correlation with recall was strongest when repetition effects during the N400(m) time window were combined for both congruent and incongruent items. This may reflect increased power due to twice as much data, and/or indicate that improved recall was associated with greater facilitation of semantic search

by priming (Kutas & Federmeier, 2000), regardless of whether or not there was also facilitation by a congruent semantic context.

10.1.3 P600(m) congruent repetition effect

In keeping with the EEG literature (Olichney, et al., 2000; Van Petten, et al., 1991), from approximately 500ms after onset of the visual word, EEG positivity and MEG magnitude were reduced upon repeat presentation of congruent items relative to their initial presentation. The EEG congruent repetition effect had a widespread bilateral parietal distribution, with significant right-lateralisation in mastoid-referenced data, despite previous studies that have inconsistently reported left-lateralisation (Olichney, et al., 2000; Van Petten, et al., 1991). In MEG, the congruent repetition effect showed a left-sided posterior temporal emphasis, but was not significantly left-lateralised.

Greater congruent repetition effect magnitude was associated with better memory performance, as reported by many other authors and in keeping with the interpretation that the P600 component reflects an individual's episodic memory ability (Besson, et al., 1992; Olichney, et al., 2006; Olichney, Morris, et al., 2002; Olichney, et al., 2000; Van Petten, et al., 1991). Like the N400m repetition effect, the relationship with recall performance was strongest when congruent and incongruent repetition effects were combined, indicating that, as expected, it plays a role in episodic memory encoding regardless of item congruency.

10.1.4 Early effects of repetition

Unexpectedly, an earlier congruency-indifferent repetition effect, with smaller responses to repeated stimuli, emerged at around 150ms in MEG. This had a left-lateralised posterior distribution that was spatially distinct from the incongruent repetition effect and congruent repetition effect, and it again correlated positively with subsequent memory performance. Although repetition effects in this time range have been reported in M/EEG before, they have not been linked with subsequent memory (Dhond, Buckner, Dale, Marinkovic, & Halgren, 2001; Henson, et al., 2004; Marinkovic, et al., 2003; McDonald, et al., 2010; Van Petten, et al., 1991).

Highlighting the reference-dependency of EEG, nose- (but not mastoid-) referenced EEG data also revealed a main effect of repetition, in the same direction as the incongruent repetition effect. However, this had significantly later latency than the MEG

effect, beginning at approximately 250ms, making it unclear whether it was the same effect.

The early repetition effect in MEG did not show evidence for sensitivity to repetition lag, persisting even across inter-item lags of 3 trials. Together with its insensitivity to congruency, this suggests that it reflected perceptual priming of the visual words, similar to previous interpretations in the EEG literature (Henson, et al., 2004; McDonald, et al., 2010; Van Petten, et al., 1991).

10.2 Active memory paradigm in healthy older controls

Chapter 3 examined the impact of age upon the presence and spatio-temporal distribution of the above MEG effects of interest. We aimed to identify spatio-temporal regions of interest (ROIs) in which effects of interest were maximal, and which would therefore be likely to be most sensitive for subsequent comparisons with clinical populations. The comparison with the younger group was used to evaluate effects of age, but most importantly to define ROIs, where possible, that were based upon maxima in the younger group data. However, when latency or location of younger group ROIs were sub-optimal for capturing the maximal effect of interest in the older group (where significant group differences existed), these were adjusted to optimise sensitivity to the effect in older aged individuals.

10.2.1 Behavioural performance

The lack of a deficit on the cued recall task in the older relative to young control group was contrary to expectations. One reason may simply be a lack of statistical power; another may be that the older controls represented an above-average sample from the population (given that they were self-selected to the CBU's participant panel). Another possibility is that age-related memory deficits would be more apparent on a test of free recall, rather than cued-recall, given that free recall has less "environmental support" (Craik, Byrd, & Swanson, 1987). Unfortunately we did not obtain free recall data from the older group, due to perceived time constraints. Indeed, the absence of a free recall test may have been a further reason for a lack of difference between groups, in that the young group's cued recall performance may have been reduced by output interference from their prior free recall test (Levy & Anderson, 2002).

10.2.2 Latency delay of N400m congruency and incongruent repetition effects

Delays in the region of 50ms were evident for both congruency effect and incongruent repetition effect in the older relative to younger individuals, in keeping with previous EEG findings (Federmeier & Kutas, 2005; Kutas & Iragui, 1998). That an effect of latency occurred only for N400m effects (not congruent repetition effect or early repetition effect) is interesting, because it suggested that these delays were not simply reflective of some global slowing with age, but rather a specific slowing in semantic retrieval. The temporal window of interest was adjusted to 400-600ms for subsequent comparisons between patient and age-matched control groups.

10.2.3 Topographical differences

10.2.3.1 N400m effects

For N400m effects, the left-sided emphasis did not differ according to age. In the gradiometer data, the older group showed lesser magnitude difference between fronto-temporal and posterior temporal ROIs than the younger group for both congruency effect and incongruent repetition effect. Given the lack of absolute magnitude differences at any individual ROI, this provided only tentative support for a posterior-to-anterior shift of processing with ageing, as suggested by prior review of the fMRI and PET ageing literature (Davis, et al., 2008), which is hypothesized to reflect strategic compensation mechanisms (Buckner, 2004; Reuter-Lorenz & Cappell, 2008).

10.2.3.2 P600m congruent repetition effect

The congruent repetition effect appeared more diffuse in the older than younger age group, possibly reflective of recruitment of more widespread neuronal populations. There were, however, no absolute magnitude differences at the ROIs which were defined from the younger group maxima. It can therefore be concluded that the reduction of P600m with repetition, a component attributed to episodic memory processes (Van Petten, et al., 1991), was equivalent in both age groups, at least across the range of repetition lags used here.

10.2.3.3 Early repetition effect

The MEG early repetition effect was robust across both age groups and SPM maxima were identical in gradiometers. The younger group's tendency towards left-hemispheric emphasis was not statistically significant in the older group. However, marked

topographical differences according to age group were evident in magnetometers, with mid-temporal maxima of significantly greater magnitude than posterior-temporal maxima in the older group, whilst the opposite was true for younger participants. Magnetometer topographies, with peak signal magnitude detected distal to, and sensitive to the orientation of, an underlying cortical source, are more difficult to interpret than planar gradiometer topographies. It is possible that this age effect in the magnetometers but not gradiometers was driven by differences in orientation but not location of the underlying early repetition effect source, perhaps due to anatomical changes such as cortical thinning with age (Salat, et al., 2004). Although selection of magnetometer ROIs defined from the older, but not younger, group maxima potentially biased subsequent comparisons with the patients, the older group maxima were selected in order to ascertain that patient-control comparisons were made at ROIs where the early repetition effect was normatively maximal.

10.3 Active memory paradigm in probable Alzheimer's disease patients

Chapter 4 developed 2 metrics, a logistic regression (LR) model and a '10^{th} percentile metric', that demonstrated the ability to classify patients with a diagnosis of mild pAD (pAD group) and the age-matched healthy control group of chapter 3 (control group). These active paradigm MEG effects of interest were believed to reflect neurophysiological counterparts of semantic (congruency effect/incongruent repetition effect), episodic (congruent repetition effect) and possibly perceptual (early repetition effect) memory processes. Although we based the classification methods upon ROIs that significantly differed between pAD and control groups, which biased these classification methods towards above-chance performance, this was not the case for the more important tests of these classification metrics in the larger patient group in the subsequent chapter.

10.3.1 Behavioural performance

Some patients performed less accurately than controls on the MEG congruency task, therefore data from all trials were incorporated into analyses for this group. Free recall was at floor in the patient group (as expected from their impaired ACE-R scores). The patient group performed above floor on the subsequent cued recall task, though still well below the control group. Although the patient group attempted the cued recall test after the free recall test (unlike the controls), which might have produced some output

interference, this is unlikely to have been the only cause of such a large impairment in their cued recall relative to the controls.

10.3.2 N400m congruency effect

As reported in the EEG literature (Iragui, et al., 1996; Schwartz, et al., 1996), congruency effect magnitude was reduced for patients relative to controls in magnetometers, indicative of reduced facilitation of semantic search via congruent context. In addition to a relatively larger N400m component (measured against pre-stimulus baseline) to congruent items, the N400m component for incongruent items appeared diminished, implying failure of underlying N400m generators, perhaps reflective of a general impairment in semantic processing.

An outlier prevented the difference in congruency effect magnitude from attaining significance in gradiometers, despite the near absence of an effect in 5 out of 8 patients. Nonetheless, this ROI was retained for further analyses to assess whether it had predictive value, along with 3 magnetometer ROIs. No significant group latency differences were identified, despite reports that EEG congruency effect latency may index memory impairment in pAD (Iragui, et al., 1996).

Two approaches were taken in devising MEG metrics that could distinguish between pAD patients and controls: 1) 10^{th} percentile cut-off thresholds, as applied in the EEG study of pAD patients that used this paradigm (Olichney, et al., 2006), and 2) a backwards step-wise logistic regression (LR) procedure. Using 10^{th} percentile thresholds, which necessarily conferred 92.9% specificity for all measures, the gradiometer ROI offered greatest sensitivity to pAD at 62.5%. The congruency effect LR model retained 2 magnetometer ROIs with equivalent specificity but, surprisingly, only 50% sensitivity to pAD. It is probable that despite the higher sensitivity of the gradiometer ROI using a cut-off threshold, the prominent outlier had undue influence on the slope of the regression line for this predictor, making it a poor fit and causing it to be rejected by the backwards step-wise LR procedure.

10.3.3 N400m incongruent repetition effect

The EEG incongruent repetition effect has been shown to be reduced in patients with pAD (Olichney, et al., 2006; Schnyer, Allen, Kaszniak, & Forster, 1999), indicative of reduced ability for semantic search to benefit from repetition. The anticipated magnitude decrement in patients was not as marked as expected given previous EEG research,

although the overall trend was in keeping with this expectation. Instead we found high variability in incongruent repetition effect magnitude, particularly within the patient group, such that only 1 magnetometer ROI significantly differed in magnitude between groups; this was carried forward for further analyses. Latency measures were equivalent across groups. The 10th percentile cut-off threshold conferred sensitivity at 50%, whilst the LR model based upon this single predictor offered equivalent specificity and higher sensitivity (62.5%).

10.3.4 P600m congruent repetition effect

The pAD patients exhibited reduced congruent repetition effect magnitude relative to controls, as reported for its EEG counterpart and attributed to diminished episodic memory function associated with medial temporal lobe atrophy (Olichney, et al., 2006; Tendolkar, et al., 1999). The pAD group also demonstrated later FAL at one ROI, likely to result from the diminution of the effect, given dependency of FAL upon magnitude. Nonetheless, the 550-800ms time window was adequate to capture the magnitude of the congruent repetition effect. Of three ROIs retained for further analysis, the most sensitive was the left posterior temporal gradiometer ROI (CRE164g). Using 10^{th} percentile thresholds this offered 50% sensitivity to pAD, whilst the LR model which retained only that ROI offered 100% specificity and 75% sensitivity to pAD, an impressive overall accuracy of 94.4%. This accuracy was only slightly lower than that obtained from the LR model which combined 4 ROIs (see section 10.3.6).

10.3.5 Early repetition effect

The early repetition effect was severely diminished bilaterally within the pAD patient group. The original component present on ‘initial’ trials in the control group also appeared greatly reduced in the pAD group, suggesting lack of a normal response to stimuli upon initial presentation, rather than failure of perceptual priming per se; however, this reached significance only in magnetometers. Of four early repetition effect ROIs retained, 10^{th} percentile cut-off thresholding offered maximum sensitivity of 50%, whereas the LR model retained 2 ROIs as predictor variables with sensitivity increased to 62.5% but less specificity (89.3% compared to 92.9%).

10.3.6 MEG metrics

We expected that the LR procedure, as a method which iteratively derives the most accurate model from the data, would offer higher accuracy than the 10th percentile thresholding; this was the case for the majority of metrics, except for the congruency effect. For this effect of interest, 10th percentile thresholding of the gradiometer ROI offered higher overall accuracy than the LR model, which did not retain that ROI. This was most likely due to presence of a single outlier on the gradiometer measure, which had also caused the group contrast to fall short of statistical significance (section 4.2.3.2).

In summarising the above sections, the congruent repetition effect appeared to be the best biomarker, with the congruency effect, incongruent repetition effect and early repetition effect slightly less useful. Nonetheless, it was possible that a combination of these markers would be even more effective. Therefore we tested further metrics using multiple effects of interest, and for comparative purposes, compared their performance with the best obtained from EEG, which utilises 10th percentile thresholds on incongruent repetition effect and congruent repetition effect (Olichney, et al., 2006); see *Table 10.1*.

Table 10.1: Accuracy of active paradigm metrics in classifying pAD/control individuals

Metric for patient classification	Sensitivity	Specificity	Overall accuracy
EEG CRE <2.5μV (Olichney, et al., 2006)	91%	73%	81.8%
MEG CRE <10th percentile	50%	92.9%	80%
EEG IRE <0.5μV (Olichney, et al., 2006)	55%	91%	73%
MEG IRE <10th percentile	50%	92.9%	80%
EEG IRE or CRE <10th percentile (Olichney, et al., 2006)	100%	82%	90.1%
MEG IRE or CRE <10th percentile	75%	85.7%	83.3%
1+ MEG effects <10th percentile (from 4 effects of interest)	87.5%	78.6%	80.6%
2+ MEG effects < 10th percentile (from 4 effects of interest)	75%	96.4%	91.7%
Logistic Regression (4 MEG predictors)	87.5%	100%	97.2%
Logistic Regression (1 MEG predictor: CRE)	75%	100%	94.4%

* CRE=Congruent Repetition Effect; IRE=Incongruent Repetition Effect

When considering the congruent repetition effect and incongruent repetition effect individually using the same thresholding method, the MEG data offered equivalent or slightly higher overall accuracy than EEG data (c.f. rows 1-4). However EEG data was slightly more accurate than MEG for the specific combination of incongruent repetition effect and congruent repetition effect (c.f. rows 5 and 6). MEG data furnished comparable

overall accuracy when multiple effects of interest (including the early repetition effect, not reported in the previous EEG study, and the congruency effect, not found to be diagnostically useful in the previous EEG study) were considered (c.f. row 8), though with different sensitivities versus specificities. In summary, MEG was superior for specific effects of interest (early repetition effect and congruency effect), but the modalities were otherwise equivalent for the congruent repetition effect and incongruent repetition effect that were found to be diagnostically useful in the EEG modality. The LR model of the MEG data based upon four predictor variables furnished the highest overall accuracy (better than the overall accuracy of the 10^{th} percentile thresholding of the EEG congruent repetition effect and incongruent repetition effect previously reported). Nonetheless, the LR model based upon a single ROI for the congruent repetition effect alone was only slightly less accurate (cf. rows 9 and 10) and far superior to 10^{th} percentile thresholding of the EEG congruent repetition effect alone (c.f. row 1). It can be concluded that this was due to a superior classification method (logistic regression compared to 10^{th} percentile thresholding) rather than superior data (MEG versus EEG), given the equivalence of MEG and EEG when thresholding the congruent repetition effect. However, that the LR model incorporating 4 ROIs furnished only slight improvement in accuracy relative to the LR model incorporating only a single ROI suggests over-fitting of data for the combined LR model. This would mean that the method was fitting noise (and there is no reliable way to check for this with logistic regression), so the high accuracy of the combined LR model may not generalise to the MC group.

10.4 Active memory paradigm in memory clinic patients

In chapter 5, the MEG metrics derived in chapter 4 were applied to a group of individuals who reported insidious-onset subjective memory difficulties (the memory clinic, or 'MC' group), in an attempt to discriminate those likely to be experiencing incipient dementia (MCI subgroup) and those whose memory problems were likely due to other causes (WW subgroup). Although we were blind to participant's provisional diagnoses at the time of testing, an experienced clinician subsequently provided his 'best-guest' opinion based upon standard clinical data, though note that the clinician emphasised that these guesses were far from definite. Therefore, although these sub-groups were used here to assess the accuracy of the MEG metrics in classifying MCI and WW cases, no final conclusions can be drawn without longitudinal follow-up data providing more definite diagnoses. Indeed,

our ultimate goal would be to identify those cases that go on to develop dementia, as opposed to those that fell into the 'high-risk' MCI classification.

Using only ROIs identified as significantly differing in independent data for older controls versus pAD patients in chapter 4, we first reported basic differences between the MC and control/pAD groups, then reported correlations of these MEG effects with measures of recall performance for MEG task items and with the ACE-R test battery. Furthermore, we went on to use ROC and logistic regression analyses to test the ability of the 2 MEG metrics that combine across effects of interest (LR model and 10^{th} percentile metric) to distinguish MCI and WW sub-groups. In particular, we computed a final LR model to compare the classification ability of MEG predictors relative to ACE-R predictors.

10.4.1 Individual MEG contrasts

10.4.1.1 Congruency N400m effect

Effect magnitude was significantly reduced in the MC relative to control group, with a larger average N400m component for congruent items in the MC group indicating some inefficiency in retrieval that resulted in reduced ability for semantic search to benefit from congruent context. This differed from the profile in the pAD group that had an additional diminution of the N400m for incongruent items, which may be explicable by degradation of semantic representations. Magnitude of the congruency effect correlated positively with cued recall and with ACE-R total, plus verbal fluency and language sub-components, most likely reflecting a semantic deficit in those in whom this component was reduced. Despite these relationships with behavioural performance and MC-control group differences, this measure was not able to discriminate MCI and WW sub-groups significantly above chance, and did not significantly improve on the accuracy of the neuropsychology-based LR model.

10.4.1.2 Incongruent repetition N400m effect

A lack of N400m reduction by repetition at some ROIs in the MC group suggested a failure of repeated exposure to incongruent items to increase efficiency of semantic search in some MC individuals. Relationships with behaviour of this effect were similar to those for the congruency effect, again suggesting that those in whom this effect is reduced may be suffering some form of semantic deficit. Despite these associations, the

incongruent repetition effect did not predict the clinician's classifications significantly above chance.

10.4.1.3 Congruent repetition P600m effect

Effect magnitude was reduced in the MC group relative to controls, but tended to be larger than in the pAD group. Despite no significant correlation with any of the behavioural measures tested, congruent repetition effect magnitude demonstrated significantly above-chance ability to predict the clinician's classification as WW or MCI, even in addition to the neuropsychological data. The lack of relationship with behaviour was somewhat surprising given reported association of EEG effect amplitude with verbal memory ability (Olichney, Riggins, et al., 2002), but suggested potential diagnostic utility beyond that offered by behavioural testing.

10.4.1.4 Early main repetition effect

In the gradiometer data, early repetition effect magnitude was significantly reduced over the left hemisphere only in the MC group relative to controls, whilst the right hemisphere reduction seen in pAD patients was not seen for the MC group. Nonetheless, it was the right, not left, hemisphere gradiometer ROI, RE242g, that significantly correlated with MC group performance on the ACE-R memory sub-component, and that displayed a cluster of high memory-performing, high effect magnitude WW-cases, in contrast with a mixed MCI/WW low-performing/low magnitude cluster.

These findings implied that pathology underlying incipient dementia impacted first upon left hemispheric sources of the early repetition effect, but it was subsequent bilateral spread that was associated with decline in mnemonic abilities, although this may be coincidental rather than causative. Given that the effect was left-lateralised in younger individuals, but that lateralisation was no longer significant in older controls, this correlation may have reflected a more general decline in the MC group of right hemispheric compensation mechanisms. In keeping with this pattern is the report that whilst visual perceptual thresholds are increased in MCI, this does not affect memory performance; however in pAD visual short term (iconic) memory deficits additionally arise (Bublak, et al., 2009). However, early repetition effect predictor variables, despite their retention in the pAD/control LR model and their relationship with memory performance in the MC group, were not able to predict the clinician's classifications significantly above chance, nor were they retained in LR models.

10.4.2 MEG metrics devised via control and pAD group data

Both of the combined MEG metrics devised in the previous chapter significantly correlated with behavioural measures of memory (although memory also suffers in affective disorders, which may be present in our WW cases), and particularly with the most robust measure of MCI-classification, total ACE-R score. However only the 10th percentile MEG metric demonstrated clustering according to, and was able to predict, those who were classified as MCI versus WW by the clinician, where the LR model was not able. This was surprising, as the LR model would be expected to be more finely-tuned to differences in pAD data than cut-off thresholds alone. It is possible that this was a symptom of over-fitting of the LR model to the pAD/control group data; as noted in the previous chapter, the addition of 3 additional predictor variables to the LR model for the congruent repetition effect only conferred only a minor increase in overall accuracy in classifying pAD cases. Such an over-fitted model would fail to accurately generalise to group membership in an independent dataset.

10.4.3 Ability of MEG data to improve upon diagnostic accuracy of behavioural tests

Considering the neuropsychology-only MC group LR model, total ACE-R score was the single significant predictor of MCI classification, with overall accuracy of 76.7%, although sensitivity was low, correctly classifying only 37.5% (3/8) of MCI cases. Using the established cut-off threshold of 88 (Mioshi, et al., 2006; Mitchell, et al., 2009), overall accuracy was equivalent, but sensitivity was much greater at 75% (6/8) whilst specificity was slightly reduced at 77.2% (17/22). This demonstrates how the imbalanced proportions of MCI/WW cases within the MC group biased the LR models towards maximising specificity over sensitivity, as the method aims to maximise overall accuracy. When a sample is comprised of a disproportionately large number of one group, the model would be more accurate when it correctly classified a given percentage of members of the larger group, than when it correctly classified a similar percentage of those from the smaller group. Had the distribution of cases been more balanced, the metric would have been influenced more towards optimising both sensitivity and specificity.

Only a single MEG predictor variable, the congruent repetition effect ROI CRE164g, was able to improve accuracy (with marginal significance of p=.052) when

added to the ACE-R total score predictor, correctly identifying one additional MCI case, with resultant overall accuracy of 78.6% (sensitivity=50%, specificity=90%). Although a modest enhancement in sensitivity, this demonstrated that the active MEG paradigm was able to improve diagnostic accuracy beyond that of behavioural testing alone, rather than reflecting information already available, and thus may be valuable to a clinician.

As noted above, the clinician was not certain of the diagnoses, providing only his provisional opinion. Tests of the utility of these metrics would optimally be conducted after longitudinal follow-up of these patients over the next few years to establish who goes on to be diagnosed with probable Alzheimer's disease. Therefore, a more definitive conclusion regarding the utility of MEG data from the present active memory paradigm to assist earlier detection of incipient dementia awaits future investigation.

10.5 Passive linguistic oddball paradigm in healthy young individuals

In chapters 6-9 we switched to a modified version of a passive linguistic oddball paradigm to investigate automatic responses able to tap into acoustic/phonetic parsing processes and long-term memory traces for words. The advantages of this pre-attentive, task-free paradigm in clinical populations include simplicity and freedom from strategic confounds. We focused on the effects of psycholinguistic variables reflecting phonological/acoustic, lexical/semantic and morphosyntactic processes upon two responses: the MMNm and the M50d (deviant-elicited P50m minus ongoing responses to standard stem stimuli).

10.5.1 Sensory gating and sensory memory (main M50d and MMNm responses)

P50(m) responses have not before been investigated in the context of speech stimuli. Our paradigm was designed to maximise the M50d by setting the average deviant ISI at 10s, as per Boutros et al. (1995), and the minimum deviant ISI at 5s. In this young group, M50d responses were statistically confirmed only in magnetometer data for */t/* plosives, although they appeared evident in the group average time courses for both plosives and sensor types. The P50(m) to repeated stimuli is typically small in young healthy individuals, but tends to be larger in older individuals who would constitute the control group for our patient comparisons (Patterson, et al., 2008).

Reliable MMNm responses beginning at around 90ms and persisting beyond 150ms were identified for both plosive types, providing robust indices of sensory memory

within this young healthy cohort and solid bases upon which to explore the psycholinguistic effects of interest.

10.5.2 Phonological/acoustic processing

A magnitude advantage of */t/* over */d/* plosives for both M50d and MMNm responses held across all stem contexts. Whilst the impact of deviance magnitude upon P50/m in oddball paradigms has not been previously explored, increased magnitude and reduced latency of the MMN have been shown to result from greater stimulus contrast, making the deviant stimulus more salient (Gaeta, et al., 1999).

In terms of acoustic properties, power differences between plosives in the current study were relatively small, but the reduced closure period before onset of a /d/ relative to /t/ plosive meant that there was increased 'forward masking' during responses to */d/*, as a result of ongoing processing of the preceding stem (Alves-Pinto, Baudoux, Palmer, & Sumner, 2010). Greater underlying activity may have effectively masked the activity evoked by */d/* more so than for */t/*. With regard to phonological properties, consistency of voicing between stem and final plosive makes the plosive less salient and more difficult to detect than in cases where voicing is inconsistent (Bird, et al., 2003). In the current stimulus set, all */d/* plosives were consistent in voicing with their preceding stems and all */t/* plosives were inconsistent. Furthermore, acoustic and phonetic features and processes are closely intertwined and it is not a trivial task to separate these two facets of speech. The finding of a */t/* magnitude advantage therefore likely reflected greater 'salience' of */t/* than */d/*; this could be acoustic and/or phonological in origin.

A trend towards greater */d/-/t/* differences in response magnitude over the right than left hemisphere may be explicable in terms of the greatest cortical masking effect over left temporal regions. Left temporal activation may have reached 'ceiling' in all plosive-ending trials, leaving little scope for modulation by plosive-type. However, this argument was unsupported by any significant interactions between hemisphere and plosive-type in the stem-only condition.

10.5.3 Lexical/semantic processing

Contrary to expectations, there were no significant differences in magnitude of MMNm responses to word and nonword stems, whereas previous studies have reported an enhanced MMN over the left hemisphere, and subsequent increased left lateralisation, for word stem-plosive combinations relative to those for pseudowords (Pulvermuller, et al.,

2001; Shtyrov, et al., 2010). A possible explanation for the lack of such an effect in the current data is that in these previous studies the word/nonword status ('wordness') of the deviant stimulus was not evident until the plosive occurred, whereas in the current study word/nonword status was highly predictable in the stem context, as was the regularity (but not identity) of deviant stimulus occurrence. This may have resulted in a 'priming' effect which reduced the usual word/nonword effect size, or possibly shifted the effect to an earlier time window. With respect to the latter, given the small magnitude of M50d responses in this younger group, any lexicality-mediated effects during this earlier time frame would be difficult to detect (see evidence in support of this suggestion in section 10.6.4).

10.5.4 Morpho-syntactic processing

Greater inter-hemispheric differences for the MMNm in gradiometers existed for 'past' contexts, where /d/ was a real or potential regular past tense grammatical suffix (*'played'* and pseudoword *'kwayed'*) than where it was not ('*trade*' and 'noise+*ed*' conditions). The LQ, a normalised laterality measure subverted the potential confound of increased magnitude for */t/* responses and revealed significantly greater left lateralisation for */d/* than */t/* plosives only in 'past' contexts. This finding suggested that grammatical parsing of regular verbs takes place during this early time window and involves a greater extent of left relative to right temporal lobe processing. As the effect was not observed for *'trade'*, which is phonologically similar to regular past tense verbs but the */d/* serves no grammatical function (although it changes the semantic meaning of the word), this does not support modified dual mechanism accounts of inflectional processing whereby parsing of *any* potentially suffixed word is postulated to occur obligatorily (Marslen-Wilson & Tyler, 2007). These findings are however consistent with both a dual mechanism account whereby the presence of a lexical representation of a full-form word ending in */d/* prevents the parsing procedure (Pinker & Ullman, 2002), and with a single mechanism account that proposes an integrated probabilistic procedure that employs phonological and semantic knowledge simultaneously (McClelland & Patterson, 2002; Woollams, et al., 2009).

10.6 Passive linguistic oddball paradigm in healthy older controls

In chapter 7, the passive linguistic paradigm was replicated in a group of neurologically healthy older individuals. We confirmed the applicability of the spatio-temporal ROIs

identified in chapter 6 to this older group and explored the impact of age upon the effects under investigation. Most importantly, we accrued control data upon which to base subsequent comparisons with patient groups.

10.6.1 Sensory gating

M50d was increased in magnitude and delayed in latency relative to the younger group. A larger P50 and its magnetic counterpart with increased age has been widely reported (Amenedo & Diaz, 1998; Golob, et al., 2007; Pekkonen, et al., 1995; Soros, et al., 2009), as has increased P50 sensory-gating ratio, reflecting reduced inhibition upon repetition of an item and interpreted as decreased ability to 'gate-out' irrelevant stimuli (Patterson, et al., 2008). Such changes can result from a reduction in cholinergic inhibition, which may arise via loss of muscarinic receptors with age (Pekkonen, et al., 2001; Pekkonen, et al., 2005).

The overall increased magnitude of M50d responses in older individuals conferred greater ability to probe effects of psycho-linguistic variables during this early time window, in comparison to younger participants whose M50d was markedly smaller and only significant for one of the two plosives.

10.6.2 Sensory memory

Magnitude of MMNm was reduced in the older relative to younger group; reduction of MMN(m) magnitude in older individuals has been reported previously, although not specifically with language stimuli (Czigler, et al., 1992; Kiang, et al., 2009; Schiff, et al., 2008). These findings possibly reflect weaker sensory memory traces (Czigler, et al., 1992; Schiff, et al., 2008) and here were replicated in the context of naturalistic speech stimuli. This previous work has indicated that age-related MMN(m) magnitude differences are not accounted for by the underlying N1(m)responses, thus it appears reasonable to interpret the smaller MMNm as reflective of reduced efficiency of pre-attentive sensory memory in older individuals.

10.6.3 Phonological/acoustic processing

For the older participants, as observed in the younger group, difference responses during both the M50d (35-65ms) and MMNm (110-150ms) time windows were consistently larger for */t/* than */d/* plosive endings. There was an interaction with group during the M50d response only, such that the */t/* - */d/* magnitude advantage was greater in older than

younger individuals. This finding is in keeping with the interpretation that whilst M50d, like the P50(m), reflects a 'signal detection' function (Boutros & Belger, 1999; Boutros, et al., 1995) whose enhancement in older age increases linearly with acoustic/phonological parameters; the decline of MMNm with older age is dependent upon a sensory memory trace (Czigler, et al., 1992; Schiff, et al., 2008) and therefore influenced to a lesser extent by purely acoustic/phonological parameters.

10.6.4 Lexical/semantic processing

M50d responses in gradiometers were enhanced for nonword relative to word contexts on the right hemisphere and were significantly more right-lateralised. Such early effects of lexicality have not been reported previously, although notably the P50(m) response is less prominent in younger individuals, who are used as participants in the majority of studies. Whereas overall increased M50d magnitude in older individuals may be due to reduced ability to 'gate out' irrelevant information, enhancement of the M50d for nonwords relative to that for words may reflect 'gating-in' of less frequent (in the sense that they do not exist in the language) and potentially more salient stimuli. Such a 'gating-in' effect has been reported previously for infrequently relative to frequently repeated non-linguistic stimuli (Boutros, et al., 1995; Rosburg, et al., 2004). The current finding implies that P50(m) gating is responsive both to current contextual salience (i.e. how recently an identical stimulus was experienced) and to larger contextual salience based upon a lifetime's experiences of language which would rely upon long-term memory representations.

The left lateralisation of this lexicality effect replicated that found previously during the later MMNm time window (Pulvermuller, et al., 2001; Shtyrov, et al., 2010; Shtyrov, et al., 2005). This shift of lexicality effects to an earlier time frame may be the consequence of our modifications to the oddball paradigm that lead to higher stimulus predictability than in conventional MMN designs; both in terms of 1) regularity of deviance occurrence and 2) that all deviants within a word context were words, whereas all those within a nonword context were nonwords.

10.6.5 Morpho-syntactic processing

There was no evidence for differential morpho-syntactic processing according to age group, and the finding of greater MMNm left lateralisation for */d/* than */t/* plosives in 'past' stem contexts replicated that identified in the younger group. This was further

supported within the older group by increased left hemisphere response magnitudes for '*played*' (a regular past-tense verb form) relative to '*trade*' (a morphological twin word where */d/* serves no grammatical function). Therefore it can be concluded that lateralisation of automatic grammatical parsing of the regular past tense was equivalent in older and younger healthy individuals.

10.7 Passive linguistic oddball paradigm in probable Alzheimer's disease patients

Chapter 8 used logistic regression and 10th percentile thresholding methods to develop passive paradigm MEG metrics able to classify pAD patients and the age-matched controls whose data were reported in chapter 7. The MEG measures we investigated were able to tap into long term memory traces for words and reflected both acoustic/phonetic and linguistic aspects of speech processing. As the responses under investigation were pre-attentive, there were no confounds of strategy, and the passive nature of the paradigm meant that patients were not stressed by the need to perform a task. The metrics were constructed from ROIs that significantly differed between the pAD and control groups which, as noted in section 10.3, biased them towards above chance performance. However, the purpose of developing these metrics was for their subsequent application to the larger memory clinic patient group in the following chapter.

Accuracy of the MEG measures and devised metrics are listed in *Table 10.2* below. Accuracy levels in classifying pAD and control groups were comparable with those for metrics devised from the active paradigm data; particularly impressive accuracy was obtained using the 10th percentile metric, which combined 5 measures (95.7%, c.f. row 4). The most accurate passive paradigm metric based upon a single predictor was the morpho-syntactic LR model (91.3%, c.f. row 6), similar to the accuracy of the congruent repetition effect active paradigm predictor (94.4%, c.f. *Table 10.1* - row 7).

10.7.1 Sensory gating

Increased M50d response magnitudes were increased in the pAD relative to control group, as anticipated from literature utilising non-linguistic stimuli (Golob, et al., 2001; Jessen, et al., 2001; Thomas, et al., 2010). Earlier M50d FAL in the pAD group relative to controls was marked yet unexpected; group waveforms suggested that a steeper rising slope rather than earlier onset of the M50d response in patients was responsible for this effect. Earlier FAL and increased magnitude likely both reflected the same 'increased

peakedness' of the M50d, supporting the interpretation of less effective sensory gating in pAD patients.

Table 10.2: Accuracy of passive paradigm metrics in classifying pAD and control individuals

Metric for patient classification	Sensitivity	Specificity	Overall accuracy
1+ MEG effects < 10th percentile (2 sensory gating measures)	62.5%	80.0%	73.9%
1+ MEG effects < 10th percentile (1 sensory memory measure)	62.5%	93.3%	82.6%
1+ MEG effects <10th percentile (1 morpho-syntactic measure)	87.5%	93.3%	91.3%
2+ MEG effects < 10th percentile (5 MEG measures)	87.5%	100%	95.7%
Sensory LR model 2 MEG predictors	75.0%	93.3%	87.0%
Morpho-syntactic LR model 1 MEG predictor	87.5%	93.3%	91.3%

Using 10th percentile thresholds, M50d magnitude and latency each conferred a maximum of 50% sensitivity to pAD. When magnitude and latency measures were combined with the requirement that both should be within the normal range for an individual to be classified as a control, sensitivity increased to 62.5% whilst specificity dropped to 80%. The sensory gating LR model retained only FAL pooled across gradiometer SOIs (M50d_FALg) with the same level of accuracy as obtained with the 10th percentile threshold for this variable.

10.7.2 Sensory memory

Reduced MMNm magnitude in patients relative to controls was significant for */t/* plosives only, although the pattern for */d/* plosives was in the same direction and there was no interaction of group with plosive (see section 10.7.3). Although reported in the (non-linguistic) MMN literature at longer inter-stimulus intervals and attributed to more rapid decay of sensory memory representations, magnitude reduction in pAD patients has not previously been found at an ISI of one second as used here but rather becomes more marked with increased ISI (Pekkonen, et al., 1994). The linguistic features of the current paradigm may have been crucial in finding this effect; as linguistic contrasts are believed to recruit long-term (as well as shorter-term) memory processes (Shtyrov, Kimppa,

Pulvermuller, & Kujala, 2011) they likely provide a more sensitive measure of memory impairment.

The application of 10th percentile cut-offs produced sensitivity of 50% for MMNm magnitude to */t/* plosives, whilst application of the LR method produced a sensory memory model with greater sensitivity than the 10th percentile metric but lower overall accuracy. A large proportion of individuals (~30%) fell close to the classification cut-off of 50%, indicating that this predictor alone was not particularly reliable in discriminating the groups.

10.7.3 Phonological/acoustic processing

There was no evidence for differential phonological/acoustic processing between the pAD and control groups. Therefore such effects were not explored further.

10.7.4 Lexical/semantic processing

As predicted, the increase of magnitude and of right hemispheric lateralisation during the M50d for nonword relative to word contexts observed in controls was not evident in the patient group, although high intra-group variability meant that a group difference was not significant. Lower SNR for the pseudoword block in the pAD relative to control group was significant in magnetometers only, so cannot account for the lack of effect in gradiometers. It is possible that in a sub-set of patients with semantic deficits (Adlam, et al., 2006; Grundman, et al., 2004; Perry, et al., 2000) there was some reduction in saliency differences of words and nonwords, with the result that nonwords were not selectively 'gated-in' (Boutros & Belger, 1999; Rosburg, et al., 2004) in these individuals. Given the pre-attentive nature of the M50d, it is most likely that this lexicality-based difference was attributable to degradation of, and/or faulty *automatic* access to, lexical/semantic representations, rather than ineffective intentional retrieval.

Lack of a main effect of group may have reflected that lexico-semantic impairment was not consistent within the group as a whole. Indeed, using 10th percentile cut-off thresholds, the most accurate predictor (NW241m) offered only 50% sensitivity to pAD. No lexicality-based measures were retained as significant predictors in LR models when combined with the other measures investigated in this paradigm. Diagnostic value of this particular lexical/semantic effect therefore appeared limited.

10.7.5 Morpho-syntactic processing

In the patient but not control group, the MMNm response to *'trade'*, a morphological twin to *'played'* but with no grammatical function for the final */d/* was significantly delayed. This finding implies that the patients may have had difficulty in resolving a conflict between semantic and phonological information, reflected in the longer latency of the MMNm to this stimulus only. For patients, like controls, the MMNm in 'past' contexts displayed */d/-/t/* laterality differences, implying preserved morphological decomposition; this was not the case for the *'tray'* context, suggesting that the */d/* in '*trade*' was not processed as a regular past tense suffix. This supports the interpretation that increases in this measure did not represent failure of the system per se, but rather less efficient processing, at least in the mildly affected patients tested here.

The likely source of this processing delay was in fact a difficulty in inhibiting interference from conflicting signals (i.e. an attempt to suppress the possible decomposition into '*tray*'+'*ed*'), as suggested by several authors (Cortese, et al., 2006; Perry & Hodges, 1999; Perry, et al., 2000), although the automatic nature of the responses we report places this difficulty firmly within pre-attentive stages of processing. Such difficulties are likely to underlie more general deficits in language processing that occur in pAD (Mathuranath, et al., 2000; Mioshi, et al., 2006).This pre-attentive effect could also reflect a general impairment in inhibitory mechanisms that might precede more overt attentional problems, which have been reported even in early stages of AD (Perry & Hodges, 1999; Perry, et al., 2000). It may also be an early marker of diminished functionality of prefrontal cortex, resulting from loss of noradrenergic innervation (Friedman, et al., 1999).

This single measure of MMNm *trade/trait* FAL difference demonstrated high accuracy in distinguishing patients with pAD from controls, with sensitivity at 87.5% (7/8) and specificity at 93.3% (14/15) whether using the 10^{th} percentile thresholding or logistic regression method.

10.7.6 MEG combined metrics

The final 10^{th} percentile metric combined all 5 measures that demonstrated sensitivity of at least 50%, with the requirement that no more than 1 measure be 'abnormal' for the individual to be classified as 'normal', gave 87.5% sensitivity and 96.2% (25/26). Although we acknowledge that these measures were biased towards above-chance performance, this level of accuracy was quite impressive.

Significant predictors remaining from backwards step-wise logistic regression of individual effects of interest were M50d latency, MMNm magnitude and MMNm *trade/trait* latency difference; however attempts to combine these into a single model resulted in perfect separation of the groups. This meant that despite 100% accuracy no unique solution could be reached, as there were multiple curves that would fit the data with equal residual variance (i.e. zero) and was likely a symptom of over-fitting to the data. This emphasises one of the shortcomings of the LR method. Therefore, 2 logistic regression models were derived, the 'sensory model' combined main M50d and MMNm effects, pertaining to sensory gating and sensory memory processes, with overall accuracy of 87.0%. The second model incorporated 'linguistic' predictors; the lexico-semantic predictor variable was excluded and only the morpho-syntactic *trade/trait* FAL difference was retained, reproducing the morpho-syntactic LR model described in section 10.7.5. Both of these passive paradigm LR models demonstrated high levels of accuracy in distinguishing pAD and control groups and were comprised of fewer variables than the active paradigm combined model (making the possibility of over-fitting to the data less likely). The *trade/trait* FAL difference measure (morpho-syntactic LR model) misclassified only two cases and showed promise as a highly accurate single predictor.

10.8 Passive linguistic oddball paradigm in memory clinic patients

Chapter 9 applied the passive MEG paradigm to memory clinic patients who participated in the active memory paradigm (chapter 5), with the aim of distinguishing those with (MCI) and without (WW) incipient dementia. A clinician provided his provisional diagnoses subsequent to MEG testing (but without knowledge of MEG findings); notably he emphasised the uncertainty of these diagnoses. Fewer MC participants completed this second MEG session, so power for statistical analyses was reduced, particularly as data were acquired for only seven MCI-classified cases.

As in chapter 5, in this chapter we assessed only the effects and ROIs that were identified as significantly differing between pAD and control groups. We conducted group-level comparisons to give an impression of the data in the MC group as a whole, before examining relationships of these MEG measures to behavioural scores. Finally we sought to establish, via ROC and logistic regression analyses, whether any MEG measures were able to classify the MCI and WW sub-groups, and particularly if any offered greater accuracy than neuropsychological data alone. As noted previously however, our ultimate aim would be to assess these metrics' utility in predicting

conversion to dementia, which would require longitudinal follow-up. Findings are summarised and discussed below:

10.8.1 Sensory gating

M50d FAL and magnitude significantly differed between MC and pAD groups, although their distributions overlapped to an extent, particularly for the latency measure; there were no significant differences in comparison with controls. Such an overlap here and in other measures was predicted based on the pathological heterogeneity of the MC group. In spite of marked differences between groups, the M50d metric did not co-vary significantly with any behavioural measures assessed here, which may point to pathophysiological changes and/or deficits in lower-level sensory processes that the behavioural tests are not sensitive to. This is in line with previous findings in MCI patients where increased P50 magnitude was not related to specific neuropsychological test scores (Golob, et al., 2002; Irimajiri, et al., 2005). Early automatic auditory processes reflected in the M50d may already be impaired by the onset of dementia and are marked in cases of mild to moderate severity (O'Mahony, Rowan, Feely, Walsh, & Coakley, 1994), but this is not necessarily accompanied by changes in behavioural performance due to possible top-down compensation mechanisms or strategies involved in purely behavioural tasks.

10.8.2 Sensory memory

MMNm magnitude (to */t/* plosives) showed a smaller reduction in the MC than pAD group relative to controls, although the overall MC – control group difference was not significant. Given the heterogeneity of the MC group, which predominantly included otherwise healthy WW individuals, this largely fits expectations. The measure did not relate to any behavioural variables, contrary to our prediction, as MMN magnitude has been shown to relate to memory performance in schizophrenic individuals (Baldeweg, et al., 2004). A possible explanation of the current findings is that auditory sensory memory was impaired in some MC individuals, but the specific nature and extent of this impairment was not sufficient to impact upon episodic recall or the ACE-R memory sub-component, which assesses a broad variety of mnemonic functions. Explicable in a similar vein, the sensory LR model, based upon sensory gating and sensory memory measures, did not demonstrate any clear relationships with behavioural performance.

10.8.3 Lexical/semantic processes

Magnitude differences in M50d between word and nonword contexts at right hemisphere ROIs were more variable in the MC than pAD group, but on average equivalently reduced relative to controls. This lexicality effect co-varied with ACE-R verbal fluency scores (although the relationship did not survive correction for multiple comparisons), suggesting a reduced capacity to access lexico-semantic representations in those who demonstrated a reduced effect, an interpretation that also fits the trend towards an association with free recall performance. Given the composite nature of the verbal fluency score (comprised of both letter and category fluency components) and that this test taxes multiple (phonological, executive and semantic) systems, it is unclear whether this might reflect a potential relationship of the lexicality effect with semantic access or fluency more generally. The pre-attentive nature of the M50d however reflects that poorer verbal fluency was associated at least partially with deficient semantic representations and/or automatic retrieval processes (not simply impaired in executive search functions).

10.8.4 Morpho-syntactic processes

The latency difference between MMNm for '*trade*' minus '*trait*' conditions suggested a processing delay in the pAD group for *'trade'*, a condition where conflicting lexico-semantic and phonological/syntactic information must be resolved. We interpreted elevation of this measure as reflective of difficulty in suppressing the conflicting (but incorrect) signal to decompose 'trade' into '*tray*'+'*ed*'. In the MC group this measure overlapped broadly with both control and pAD groups, but overall significantly differed from both, demonstrating a group tendency for slower responses to '*trade*' than '*trait*', like the pAD group but to a lesser degree. The LR model based only upon this effect co-varied with the ACE-R language sub-component (although this did not survive correction for multiple comparisons), indicative of poorer comprehension, naming, spelling and writing abilities in those individuals who showed a greater susceptibility to this response delay associated with processing conflict. Thus this measure is likely to be sensitive to processes underlying language impairments that are reported in MCI patients (Mioshi, et al., 2006) and perhaps more so in those who will develop other variants of dementia that have more marked effect upon language abilities (Mathuranath, et al., 2000).

10.8.5 10th percentile metric

The 10th percentile metric summed number of abnormal scores from 5 of the above MEG measures for each individual. It included sensory gating, sensory memory, lexico-semantic and morpho-syntactic measures and showed relationships with behaviour that were not evident for individual effects. Most notably, correlations were evident between this metric and all behavioural indices of mnemonic ability, as well as ACE-R total and the language sub-component (although only relationships with free recall and ACE-R total score survived the stringent Bonferonni correction). There was clear clustering of 5 out of 7 MCI-classified cases who demonstrated poor performance on these behavioural measures and had a high number of abnormal MEG measures. This suggests that deterioration in multiple domains, reflected in the various MEG measures that comprised the 10th percentile metric, combined to produce detectable impairments in cognitive function.

10.8.6 Utility of MEG measures in predicting clinician's provisional diagnosis

Although some of the passive paradigm MEG metrics showed impressive performance in differentiating healthy subjects and pAD patients, none of them significantly distinguished individuals provisionally diagnosed by the clinician as MCI from those he considered to be WW. The suggestion that these metrics have nothing to offer diagnostically must be tempered slightly, firstly given the lack of power in the current analyses due to small sample sizes and, secondly, given the uncertainty of preliminary diagnoses.

Due to the unequal group sizes, improvements in overall accuracy, and therefore LR model significance, were biased towards correct negative classifications and away from identifying positive cases. As positive cases comprised less than 27% of the overall group, any increase in sensitivity had only a quarter of the impact on overall model accuracy as an equivalent percentage increase in specificity. For example, whilst the accuracy of the neuropsychology-only model resided in its high specificity, it correctly identified only one MCI case out of seven (sensitivity of 14.3%). Addition of either the morpho-syntactic predictor variable, or both M50d predictor variables increased sensitivity substantially, by a further 28.6% (3/7 correct positive classifications) and without reducing specificity. Yet given the small proportion of MCI cases, improvements in overall accuracy did not reach statistical significance. This suggests that the passive

paradigm analyses suffered from a lack of power for statistical testing, rather than that the predictors themselves are categorically not of diagnostic value.

10.9 Conclusions

The MEG measures considered here have demonstrated a trajectory of change from healthy controls, through the MC group, to those with a diagnosis of mild dementia, many of which were consistent with previous literature, though some also that were new. Although an expert clinician provided us with his *provisional* diagnoses, based upon standard clinical information (clinical interview, ACE-R test battery and in some cases a clinical MRI scan) for the MC patients, he was keen to stress that these opinions were far from certain. Therefore, although we assessed the utility of our MEG metrics against these classifications, it should be borne in mind that these constituted an imperfect benchmark.

Perhaps most importantly, these measures demonstrated their ability to clearly separate healthy individuals from diagnosed pAD patients. Potentially, this might mean that they would be more useful in distinguishing MCI patients who will progress to have AD from those who will not. This, however, was not possible within the timescale of the current research and will require a follow-up study that will address the current patient group after a passage of a few years when longitudinal information is available, enabling confirmation as to which members of the MC group were experiencing incipient dementia at the time of MEG data acquisition. At the moment, there is still hope that MEG will provide useful clinical markers for early detection of dementia.

References

Adlam, A. L., Bozeat, S., Arnold, R., Watson, P., & Hodges, J. R. (2006). Semantic knowledge in mild cognitive impairment and mild Alzheimer's disease. *Cortex, 42*(5), 675-684.

Ahlfors, S. P., Han, J., Belliveau, J. W., & Hamalainen, M. S. (2010). Sensitivity of MEG and EEG to source orientation. *Brain Topogr, 23*(3), 227-232.

Alladi, S., Arnold, R., Mitchell, J., Nestor, P. J., & Hodges, J. R. (2006). Mild cognitive impairment: applicability of research criteria in a memory clinic and characterization of cognitive profile. *Psychol Med, 36*(4), 507-515.

Alves-Pinto, A., Baudoux, S., Palmer, A. R., & Sumner, C. J. (2010). Forward masking estimated by signal detection theory analysis of neuronal responses in primary auditory cortex. *J Assoc Res Otolaryngol, 11*(3), 477-494.

Amenedo, E., & Diaz, F. (1998). Automatic and effortful processes in auditory memory reflected by event-related potentials. Age-related findings. *Electroencephalogr Clin Neurophysiol, 108*(4), 361-369.

Baldeweg, T., Klugman, A., Gruzelier, J., & Hirsch, S. R. (2004). Mismatch negativity potentials and cognitive impairment in schizophrenia. *Schizophr Res, 69*(2-3), 203-217.

Bendixen, A., Prinz, W., Horvath, J., Trujillo-Barreto, N. J., & Schroger, E. (2008). Rapid extraction of auditory feature contingencies. *Neuroimage, 41*(3), 1111-1119.

Bertoli, S., Smurzynski, J., & Probst, R. (2002). Temporal resolution in young and elderly subjects as measured by mismatch negativity and a psychoacoustic gap detection task. *Clin Neurophysiol, 113*(3), 396-406.

Besson, M., & Kutas, M. (1993). The many facets of repetition: a cued-recall and event-related potential analysis of repeating words in same versus different sentence contexts. *J Exp Psychol Learn Mem Cogn, 19*(5), 1115-1133.

Besson, M., Kutas, M., & Van Petten, C. (1992). An event-related potential ERP analysis of semantic congruity and repetition effects in sentences. *Journal of cognitive neuroscience, 4*, 132-149.

Bird, H., Lambon Ralph, M. A., Seidenberg, M. S., McClelland, J. L., & Patterson, K. (2003). Deficits in phonology and past-tense morphology: What's the connection? *Journal of memory and language, 48*, 502-526.

Boutros, N. N., & Belger, A. (1999). Midlatency evoked potentials attenuation and augmentation reflect different aspects of sensory gating. [Research Support, Non-U.S. Gov't]. *Biological psychiatry, 45*(7), 917-922.

Boutros, N. N., Torello, M. W., Barker, B. A., Tueting, P. A., Wu, S. C., & Nasrallah, H. A. (1995). The P50 evoked potential component and mismatch detection in normal volunteers: implications for the study of sensory gating. *Psychiatry Res, 57*(1), 83-88.

Braak, E., Griffing, K., Arai, K., Bohl, J., Bratzke, H., & Braak, H. (1999). Neuropathology of Alzheimer's disease: what is new since A. Alzheimer? *Eur Arch Psychiatry Clin Neurosci, 249 Suppl 3*, 14-22.

Braak, H., & Braak, E. (1991). Neuropathological stageing of Alzheimer-related changes. *Acta Neuropathol, 82*(4), 239-259.

Braff, D. L., & Geyer, M. A. (1990). Sensorimotor gating and schizophrenia. Human and animal model studies. *Arch Gen Psychiatry, 47*(2), 181-188.

Bronnick, K. S., Nordby, H., Larsen, J. P., & Aarsland, D. (2008). Disturbance of automatic auditory change detection in dementia associated with Parkinson's disease: A mismatch negativity study. *Neurobiol Aging*.

Bublak, P., Redel, P., Sorg, C., Kurz, A., Forstl, H., Muller, H. J., et al. (2009). Staged decline of visual processing capacity in mild cognitive impairment and Alzheimer's disease. *Neurobiol Aging*.

Buckner, R. L. (2004). Memory and executive function in aging and AD: multiple factors that cause decline and reserve factors that compensate. *Neuron, 44*(1), 195-208.

Burke, D. M., & Mackay, D. G. (1997). Memory, language, and ageing. *Philos Trans R Soc Lond B Biol Sci, 352*(1363), 1845-1856.

Burkhardt, P. (2007). The P600 reflects cost of new information in discourse memory. *Neuroreport, 18*(17), 1851-1854.

Cabeza, R. (2001). Cognitive neuroscience of aging: contributions of functional neuroimaging. *Scand J Psychol, 42*(3), 277-286.

Cabeza, R. (2002). Hemispheric asymmetry reduction in older adults: the HAROLD model. *Psychol Aging, 17*(1), 85-100.

Cabeza, R., Anderson, N. D., Locantore, J. K., & McIntosh, A. R. (2002). Aging gracefully: compensatory brain activity in high-performing older adults. *Neuroimage, 17*(3), 1394-1402.

Castaneda, M., Ostrosky-Solis, F., Perez, M., Bobes, M. A., & Rangel, L. E. (1997). ERP assessment of semantic memory in Alzheimer's disease. *Int J Psychophysiol, 27*(3), 201-214.

Chertkow, H., & Bub, D. (1990). Semantic memory loss in dementia of Alzheimer's type. What do various measures measure? *Brain, 113 (Pt 2)*, 397-417.

Chetelat, G., Desgranges, B., de la Sayette, V., Viader, F., Berkouk, K., Landeau, B., et al. (2003). Dissociating atrophy and hypometabolism impact on episodic memory in mild cognitive impairment. *Brain, 126*(Pt 9), 1955-1967.

Corral, M., Rodriguez, M., Amenedo, E., Sanchez, J. L., & Diaz, F. (2006). Cognitive reserve, age, and neuropsychological performance in healthy participants. *Dev Neuropsychol, 29*(3), 479-491.

Cortese, M. J., Balota, D. A., Sergent-Marshall, S. D., Buckner, R. L., & Gold, B. T. (2006). Consistency and regularity in past-tense verb generation in healthy ageing, Alzheimer's disease, and semantic dementia. *Cogn Neuropsychol, 23*(6), 856-876.

Craik, F. I., Byrd, M., & Swanson, J. M. (1987). Patterns of memory loss in three elderly samples. *Psychol Aging, 2*(1), 79-86.

Czigler, I., Csibra, G., & Csontos, A. (1992). Age and inter-stimulus interval effects on event-related potentials to frequent and infrequent auditory stimuli. *Biol Psychol, 33*(2-3), 195-206.

Davies, R. R., Dawson, K., Mioshi, E., Erzinclioglu, S., & Hodges, J. R. (2008). Differentiation of semantic dementia and Alzheimer's disease using the Addenbrooke's Cognitive Examination (ACE). *Int J Geriatr Psychiatry, 23*(4), 370-375.

Davis, S. W., Dennis, N. A., Daselaar, S. M., Fleck, M. S., & Cabeza, R. (2008). Que PASA? The posterior-anterior shift in aging. *Cereb Cortex, 18*(5), 1201-1209.

DeLong, E. R., DeLong, D. M., & Clarke-Pearson, D. L. (1988). Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. *Biometrics, 44*(3), 837-845.

Delorme, A., & Makeig, S. (2004). EEGLAB: an open source toolbox for analysis of single-trial EEG dynamics. *Journal of Neuroscience Methods, 134*, 9-21.

Dhond, R. P., Buckner, R. L., Dale, A. M., Marinkovic, K., & Halgren, E. (2001). Spatiotemporal maps of brain activity underlying word generation and their modification during repetition priming. *J Neurosci, 21*(10), 3564-3571.

Dolcos, F., Rice, H. J., & Cabeza, R. (2002). Hemispheric asymmetry and aging: right hemisphere decline or asymmetry reduction. *Neurosci Biobehav Rev, 26*(7), 819-825.

Dudas, R. B., Berrios, G. E., & Hodges, J. R. (2005). The Addenbrooke's cognitive examination (ACE) in the differential diagnosis of early dementias versus affective disorder. *Am J Geriatr Psychiatry, 13*(3), 218-226.

Dudas, R. B., Clague, F., Thompson, S. A., Graham, K. S., & Hodges, J. R. (2005). Episodic and semantic memory in mild cognitive impairment. *Neuropsychologia, 43*(9), 1266-1276.

ElektaNeuromag. (2005). Elekta Neuromag system hardware user's manual (7th ed.). Helsinki, Finland.

Ermutlu, M. N., Demiralp, T., & Karamursel, S. (2007). The effects of interstimulus interval on sensory gating and on preattentive auditory memory in the oddball paradigm. Can magnitude of the sensory gating affect preattentive auditory comparison process? *Neurosci Lett, 412*(1), 1-5.

Federmeier, K. D., & Kutas, M. (1999). Right words and left words: electrophysiological evidence for hemispheric differences in meaning processing. *Brain Res Cogn Brain Res, 8*(3), 373-392.

Federmeier, K. D., & Kutas, M. (2005). Aging in context: age-related changes in context use during language comprehension. *Psychophysiology, 42*(2), 133-141.

Fernandez, G., Heitkemper, P., Grunwald, T., Van Roost, D., Urbach, H., Pezer, N., et al. (2001). Inferior temporal stream for word processing with integrated mnemonic function. *Hum Brain Mapp, 14*(4), 251-260.

Fernandez, G., Weyerts, H., Tendolkar, I., Smid, H. G., Scholz, M., & Heinze, H. J. (1998). Event-related potentials of verbal encoding into episodic memory: dissociation between the effects of subsequent memory performance and distinctiveness. *Psychophysiology, 35*(6), 709-720.

Finnigan, S., Humphreys, M. S., Dennis, S., & Geffen, G. (2002). ERP 'old/new' effects: memory strength and decisional factor(s). *Neuropsychologia, 40*(13), 2288-2304.

Fischer, C., Luaute, J., Adeleine, P., & Morlet, D. (2004). Predictive value of sensory and cognitive evoked potentials for awakening from coma. *Neurology, 63*(4), 669-673.

Ford, J. M., Askari, N., Mathalon, D. H., Menon, V., Gabrieli, J. D., Tinklenberg, J. R., et al. (2001). Event-related brain potential evidence of spared knowledge in Alzheimer's disease. *Psychol Aging, 16*(1), 161-176.

Friederici, A. D., Hahne, A., & von Cramon, D. Y. (1998). First-pass versus second-pass parsing processes in a Wernicke's and a Broca's aphasic: electrophysiological evidence for a double dissociation. *Brain Lang, 62*(3), 311-341.

Friedman, J. I., Adler, D. N., & Davis, K. L. (1999). The role of norepinephrine in the pathophysiology of cognitive disorders: potential applications to the treatment of cognitive dysfunction in schizophrenia and Alzheimer's disease. *Biol Psychiatry, 46*(9), 1243-1252.

Friston, K. J., Penny, W., Phillips, C., Kiebel, S., Hinton, G., & Ashburner, J. (2002). Classical and Bayesian inference in neuroimaging: theory. *Neuroimage, 16*(2), 465-483.

Gaeta, H., Friedman, D., Ritter, W., & Cheng, J. (1998). An event-related potential study of age-related changes in sensitivity to stimulus deviance. *Neurobiol Aging, 19*(5), 447-459.

Gaeta, H., Friedman, D., Ritter, W., & Cheng, J. (1999). Changes in sensitivity to stimulus deviance in Alzheimer's disease: an ERP perspective. *Neuroreport, 10*(2), 281-287.

Garagnani, M., & Pulvermuller, F. (2011). From sounds to words: a neurocomputational model of adaptation, inhibition and memory processes in auditory change detection. *Neuroimage, 54*(1), 170-181.

Garagnani, M., Shtyrov, Y., & Pulvermuller, F. (2009). Effects of attention on what is known and what is not: MEG evidence for functionally discrete memory circuits. *Front Hum Neurosci, 3*, 10.

Giacobini, E. (2001). Do cholinesterase inhibitors have disease-modifying effects in Alzheimer's disease? *CNS Drugs, 15*(2), 85-91.

Gloor, P. (1985). Neuronal generators and the problem of localization in electroencephalography: Application of volume conductor theory to electroencephalography. *Journal of Clinical Neurophysiology, 2*(4), 327-355.

Golob, E. J., Irimajiri, R., & Starr, A. (2007). Auditory cortical activity in amnestic mild cognitive impairment: relationship to subtype and conversion to dementia. *Brain, 130*(Pt 3), 740-752.

Golob, E. J., Johnson, J. K., & Starr, A. (2002). Auditory event-related potentials during target detection are abnormal in mild cognitive impairment. *Clin Neurophysiol, 113*(1), 151-161.

Golob, E. J., Miranda, G. G., Johnson, J. K., & Starr, A. (2001). Sensory cortical interactions in aging, mild cognitive impairment, and Alzheimer's disease. *Neurobiol Aging, 22*(5), 755-763.

Grundman, M., Petersen, R. C., Ferris, S. H., Thomas, R. G., Aisen, P. S., Bennett, D. A., et al. (2004). Mild cognitive impairment can be distinguished from Alzheimer disease and normal aging for clinical trials. *Arch Neurol, 61*(1), 59-66.

Hagoort, P. (2008). The fractionation of spoken language understanding by measuring electrical and magnetic brain signals. *Philos Trans R Soc Lond B Biol Sci, 363*(1493), 1055-1069.

Hagoort, P., Brown, C. M., & Groothusen, J. (1993). The syntactic positive shift (SPS) as an ERP measure of syntactic processing. *Lang. cognit. Processes, 8*, 439-483.

Halgren, E., Baudena, P., Heit, G., Clarke, M., & Marinkovic, K. (1994a). Spatio-temporal stages in face and word processing. I. Depth-recorded potentials in the human occipital, temporal and parietal lobes. *J Physiol Paris, 88*(1), 1-50.

Halgren, E., Baudena, P., Heit, G., Clarke, M., Marinkovic, K., & Chauvel, P. (1994b). Spatio-temporal stages in face and word processing. 2. Depth-recorded potentials in the human frontal and rolandic cortices. *J. Physiol. (Paris), 88*, 51-80.

Halgren, E., Dhond, R. P., Christensen, N., Van Petten, C., Marinkovic, K., Lewine, J. D., et al. (2002). N400-like magnetoencephalography responses modulated by semantic context, word frequency, and lexical class in sentences. *Neuroimage, 17*(3), 1101-1116.

Hamalainen, M., Hari, R., Ilmoniemi, R., Knuutila, J., & Lounasmaa, O. (1993). Magnetoencephalography - theory, instrumentation, and applications to noninvasive studies of the working human brain. *Reviews of Modern Physics, 65*(2), 413-497.

Hamberger, M. J., Friedman, D., Ritter, W., & Rosen, J. (1995). Event-related potential and behavioral correlates of semantic processing in Alzheimer's patients and normal controls. *Brain Lang, 48*(1), 33-68.

Hari, R., Parkkonen, L., & Nangini, C. (2010). The brain in time: insights from neuromagnetic recordings. *Annals of the New York Academy of Sciences, 1191*, 89-109.

Head, D., Rodrigue, K. M., Kennedy, K. M., & Raz, N. (2008). Neuroanatomical and cognitive mediators of age-related differences in episodic memory. *Neuropsychology, 22*(4), 491-507.

Hedden, T., & Gabrieli, J. D. (2004). Insights into the ageing mind: a view from cognitive neuroscience. *Nat Rev Neurosci, 5*(2), 87-96.

Henson, R. N. (2003). Neuroimaging studies of priming. *Prog Neurobiol, 70*(1), 53-81.

Henson, R. N., Mouchlianitis, E., Matthews, W. J., & Kouider, S. (2008). Electrophysiological correlates of masked face priming. *Neuroimage, 40*(2), 884-895.

Henson, R. N., Rylands, A., Ross, E., Vuilleumeir, P., & Rugg, M. D. (2004). The effect of repetition lag on electrophysiological and haemodynamic correlates of visual object priming. *Neuroimage, 21*(4), 1674-1689.

Hughes, L. E., Nestor, P. J., Hodges, J. R., & Rowe, J. B. (2011). Magnetoencephalography of frontotemporal dementia: spatiotemporally localized changes during semantic decisions. *Brain*.

Huotilainen, M., Winkler, I., Alho, K., Escera, C., Virtanen, J., Ilmoniemi, R. J., et al. (1998). Combined mapping of human auditory EEG and MEG responses. *Electroencephalogr Clin Neurophysiol, 108*(4), 370-379.

Iragui, V., Kutas, M., & Salmon, D. P. (1996). Event-related brain potentials during semantic categorization in normal aging and senile dementia of the Alzheimer's type. *Electroencephalogr Clin Neurophysiol, 100*(5), 392-406.

Irimajiri, R., Golob, E. J., & Starr, A. (2005). Auditory brain-stem, middle- and long-latency evoked potentials in mild cognitive impairment. *Clin Neurophysiol, 116*(8), 1918-1929.

Jaaskelainen, I. P., Ahveninen, J., Bonmassar, G., Dale, A. M., Ilmoniemi, R. J., Levanen, S., et al. (2004). Human posterior auditory cortex gates novel sounds to consciousness. *Proc Natl Acad Sci U S A, 101*(17), 6809-6814.

Jessen, F., Kucharski, C., Fries, T., Papassotiropoulos, A., Hoenig, K., Maier, W., et al. (2001). Sensory gating deficit expressed by a disturbed suppression of the P50 event-related potential in patients with Alzheimer's disease. *Am J Psychiatry, 158*(8), 1319-1321.

Karas, G. B., Scheltens, P., Rombouts, S. A., Visser, P. J., van Schijndel, R. A., Fox, N. C., et al. (2004). Global and local gray matter loss in mild cognitive impairment and Alzheimer's disease. *Neuroimage, 23*(2), 708-716.

Karayanidis, F., Andrews, S., Ward, P. B., & McConaghy, N. (1991). Effects of inter-item lag on word repetition: an event-related potential study. *Psychophysiology, 28*(3), 307-318.

Kazmerski, V. A., Friedman, D., & Ritter, W. (1997). Mismatch negativity during attend and ignore conditions in Alzheimer's disease. *Biol Psychiatry, 42*(5), 382-402.

Kiang, M., Braff, D. L., Sprock, J., & Light, G. A. (2009). The relationship between preattentive sensory processing deficits and age in schizophrenia patients. *Clin Neurophysiol, 120*(11), 1949-1957.

Kiefer, M. (2002). The N400 is modulated by unconsciously perceived masked words: further evidence for an automatic spreading activation account of N400 priming effects. *Brain Res Cogn Brain Res, 13*(1), 27-39.

Knott, V., Millar, A., & Fisher, D. (2009). Sensory gating and source analysis of the auditory P50 in low and high suppressors. *Neuroimage, 44*(3), 992-1000.

Korzyukov, O., Pflieger, M. E., Wagner, M., Bowyer, S. M., Rosburg, T., Sundaresan, K., et al. (2007). Generators of the intracranial P50 response in auditory sensory gating. *Neuroimage, 35*(2), 814-826.

Kutas, M., & Federmeier, K. D. (2000). Electrophysiology reveals semantic memory use in language comprehension. *Trends Cogn Sci, 4*(12), 463-470.

Kutas, M., & Hillyard, S. A. (1982). The lateral distribution of event-related potentials during sentence processing. *Neuropsychologia, 20*, 579-590.

Kutas, M., & Iragui, V. (1998). The N400 in a semantic categorization task across 6 decades. *Electroencephalogr Clin Neurophysiol, 108*(5), 456-471.

Lambon Ralph, M. A., Powell, J., Howard, D., Whitworth, A. B., Garrard, P., & Hodges, J. R. (2001). Semantic memory is impaired in both dementia with Lewy bodies and dementia of Alzheimer's type: a comparative neuropsychological study and literature review. *J Neurol Neurosurg Psychiatry, 70*(2), 149-156.

Levy, B. J., & Anderson, M. C. (2002). Inhibitory processes and the control of memory retrieval. *Trends Cogn Sci, 6*(7), 299-305.

Lounasmaa, O. V., & Hari, R. (2003). From 1- to 306-channel magnetoencephalography in 15 years: highlights of neuromagnetic brain research in Finland. In Z.-L. Lu & L. Kaufman (Eds.), *Magnetic source imaging of the human brain* (pp. 231-242). Mahwah, NJ: Lawrence Erlbaum Associates Inc.

Lu, Z.-L., & Kaufman, L. (Eds.). (2003). *Magnetic source imaging of the human brain*. Mahwah, NJ. USA: Lawrence Erlbaum Associates, Inc.

Marinkovic, K., Dhond, R. P., Dale, A. M., Glessner, M., Carr, V., & Halgren, E. (2003). Spatiotemporal dynamics of modality-specific and supramodal word processing. *Neuron, 38*(3), 487-497.

Marslen-Wilson, W. D., & Tyler, L. K. (1975). Processing structure of sentence perception. *Nature, 257*(5529), 784-786.

Marslen-Wilson, W. D., & Tyler, L. K. (2007). Morphology, language and the brain: the decompositional substrate for language comprehension. [Research Support, Non-U.S. Gov't

Review]. *Philosophical transactions of the Royal Society of London. Series B, Biological sciences, 362*(1481), 823-836.

Mathuranath, P. S., Nestor, P. J., Berrios, G. E., Rakowicz, W., & Hodges, J. R. (2000). A brief cognitive test battery to differentiate Alzheimer's disease and frontotemporal dementia. *Neurology, 55*(11), 1613-1620.

McCarthy, G., Nobre, A. C., Bentin, S., & Spencer, D. D. (1995). Language-related field potentials in the anterior-medial temporal lobe: I. Intracranial distribution and neural generators. *J Neurosci, 15*(2), 1080-1089.

McClelland, J. L., & Patterson, K. (2002). Rules or connections in past-tense inflections: what does the evidence rule out? *Trends in cognitive sciences, 6*(11), 465-472.

McDonald, C. R., Thesen, T., Carlson, C., Blumberg, M., Girard, H. M., Trongnetrpunya, A., et al. (2010). Multimodal imaging of repetition priming: Using fMRI, MEG, and intracranial EEG to reveal spatiotemporal profiles of word processing. *Neuroimage, 53*(2), 707-717.

Mioshi, E., Dawson, K., Mitchell, J., Arnold, R., & Hodges, J. R. (2006). The Addenbrooke's Cognitive Examination Revised (ACE-R): a brief cognitive test battery for dementia screening. *Int J Geriatr Psychiatry, 21*(11), 1078-1085.

Mitchell, J., Arnold, R., Dawson, K., Nestor, P. J., & Hodges, J. R. (2009). Outcome in subgroups of mild cognitive impairment (MCI) is highly predictable using a simple algorithm. *J Neurol, 256*(9), 1500-1509.

Molins, A., Stufflebeam, S. M., Brown, E. N., & Hamalainen, M. S. (2008). Quantification of the benefit from integrating MEG and EEG data in minimum l2-norm estimation. *Neuroimage, 42*(3), 1069-1077.

Naatanen, R. (1990). The role of attention in auditory information processing as revealed by event-related potentials and other measures of cognitive function. *Behav Brain Sciences, 13*, 201-288.

Naatanen, R. (2001). The perception of speech sounds by the human brain as reflected by the mismatch negativity (MMN) and its magnetic equivalent (MMNm). *Psychophysiology, 38*(1), 1-21.

Naatanen, R., Kujala, T., & Winkler, I. (2011). Auditory processing that leads to conscious perception: a unique window to central auditory processing opened by the mismatch negativity and related responses. *Psychophysiology, 48*(1), 4-22.

Naatanen, R., Lehtokoski, A., Lennes, M., Cheour, M., Huotilainen, M., Iivonen, A., et al. (1997). Language-specific phoneme representations revealed by electric and magnetic brain responses. *Nature, 385*(6615), 432-434.

Nagy, M. E., & Rugg, M. D. (1989). Modulation of event-related potentials by word repetition: the effects of inter-item lag. *Psychophysiology, 26*(4), 431-436.

Nestor, P. J., Fryer, T. D., Ikeda, M., & Hodges, J. R. (2003). Retrosplenial cortex (BA 29/30) hypometabolism in mild cognitive impairment (prodromal Alzheimer's disease). *Eur J Neurosci, 18*(9), 2663-2667.

Nestor, P. J., Scheltens, P., & Hodges, J. R. (2004). Advances in the early detection of Alzheimer's disease. *Nat Med, 10 Suppl*, S34-41.

Nobel, P. A., & Shiffrin, R. M. (2001). Retrieval processes in recognition and cued recall. *J Exp Psychol Learn Mem Cogn, 27*(2), 384-413.

O'Mahony, D., Rowan, M., Feely, J., Walsh, J. B., & Coakley, D. (1994). Primary auditory pathway and reticular activating system dysfunction in Alzheimer's disease. *Neurology, 44*(11), 2089-2094.

Oldfield, R. C. (1971). The assessment and analysis of handedness: the Edinburgh inventory. *Neuropsychologia, 9*(1), 97-113.

Olichney, J. M., Iragui, V. J., Salmon, D. P., Riggins, B. R., Morris, S. K., & Kutas, M. (2006). Absent event-related potential (ERP) word repetition effects in mild Alzheimer's disease. *Clin Neurophysiol, 117*(6), 1319-1330.

Olichney, J. M., Morris, S. K., Ochoa, C., Salmon, D. P., Thal, L. J., Kutas, M., et al. (2002). Abnormal verbal event related potentials in mild cognitive impairment and incipient Alzheimer's disease. *J Neurol Neurosurg Psychiatry, 73*(4), 377-384.

Olichney, J. M., Riggins, B. R., Hillert, D. G., Nowacki, R., Tecoma, E., Kutas, M., et al. (2002). Reduced sensitivity of the N400 and late positive component to semantic congruity and word repetition in left temporal lobe epilepsy. *Clin Electroencephalogr, 33*(3), 111-118.

Olichney, J. M., Taylor, J. R., Chan, S., Yang, J. C., Stringfellow, A., Hillert, D. G., et al. (2010). fMRI responses to words repeated in a congruous semantic context are abnormal in mild Alzheimer's disease. *Neuropsychologia, 48*(9), 2476-2487.

Olichney, J. M., Taylor, J. R., Gatherwright, J., Salmon, D. P., Bressler, A. J., Kutas, M., et al. (2008). Patients with MCI and N400 or P600 abnormalities are at very high risk for conversion to dementia. *Neurology, 70*(19 Pt 2), 1763-1770.

Olichney, J. M., Taylor, J. R., Hillert, D. G., Chan, S. H., Salmon, D. P., Gatherwright, J., et al. (2008). fMRI congruous word repetition effects reflect memory variability in normal elderly. *Neurobiol Aging*.

Olichney, J. M., Van Petten, C., Paller, K. A., Salmon, D. P., Iragui, V. J., & Kutas, M. (2000). Word repetition in amnesia. Electrophysiological measures of impaired and spared memory. *Brain, 123 (Pt 9)*, 1948-1963.

Paavilainen, P., Arajarvi, P., & Takegata, R. (2007). Preattentive detection of nonsalient contingencies between auditory features. *Neuroreport, 18*(2), 159-163.

Paller, K. A., & Kutas, M. (1992). Brain potentials during memory retrieval provide neurophysiological support for the distinction between conscious recollection and priming. *Journal of cognitive neuroscience, 4*(375-391).

Paller, K. A., Kutas, M., & Mayes, A. R. (1987). Neural correlates of encoding in an incidental learning paradigm. *Electroencephalogr Clin Neurophysiol, 67*(4), 360-371.

Patterson, J. V., Hetrick, W. P., Boutros, N. N., Jin, Y., Sandman, C., Stern, H., et al. (2008). P50 sensory gating ratios in schizophrenics and controls: a review and data analysis. *Psychiatry Res, 158*(2), 226-247.

Pekkonen, E. (2000). Mismatch negativity in aging and in Alzheimer's and Parkinson's diseases. *Audiol Neurootol, 5*(3-4), 216-224.

Pekkonen, E., Hirvonen, J., Jaaskelainen, I. P., Kaakkola, S., & Huttunen, J. (2001). Auditory sensory memory and the cholinergic system: implications for Alzheimer's disease. *Neuroimage, 14*(2), 376-382.

Pekkonen, E., Huotilainen, M., Virtanen, J., Sinkkonen, J., Rinne, T., Ilmoniemi, R. J., et al. (1995). Age-related functional differences between auditory cortices: a whole-head MEG study. *Neuroreport, 6*(13), 1803-1806.

Pekkonen, E., Jaaskelainen, I. P., Kaakkola, S., & Ahveninen, J. (2005). Cholinergic modulation of preattentive auditory processing in aging. *Neuroimage, 27*(2), 387-392.

Pekkonen, E., Jousmaki, V., Kononen, M., Reinikainen, K., & Partanen, J. (1994). Auditory sensory memory impairment in Alzheimer's disease: an event-related potential study. *Neuroreport, 5*(18), 2537-2540.

Pekkonen, E., Jousmaki, V., Partanen, J., & Karhu, J. (1993). Mismatch negativity area and age-related auditory memory. *Electroencephalogr Clin Neurophysiol, 87*(5), 321-325.

Perry, R. J., & Hodges, J. R. (1999). Attention and executive deficits in Alzheimer's disease. A critical review. *Brain, 122 (Pt 3)*, 383-404.

Perry, R. J., Watson, P., & Hodges, J. R. (2000). The nature and staging of attention dysfunction in early (minimal and mild) Alzheimer's disease: relationship to episodic and semantic memory impairment. *Neuropsychologia, 38*(3), 252-271.

Petersen, R. C., & Negash, S. (2008). Mild cognitive impairment: an overview. *CNS Spectr, 13*(1), 45-53.

Petersen, R. C., Parisi, J. E., Dickson, D. W., Johnson, K. A., Knopman, D. S., Boeve, B. F., et al. (2006). Neuropathologic features of amnestic mild cognitive impairment. *Arch Neurol, 63*(5), 665-672.

Petersen, R. C., Roberts, R. O., Knopman, D. S., Boeve, B. F., Geda, Y. E., Ivnik, R. J., et al. (2009). Mild cognitive impairment: ten years later. *Arch Neurol, 66*(12), 1447-1455.

Pinker, S., & Ullman, M. T. (2002). The past and future of the past tense. *Trends in cognitive sciences, 6*(11), 456-463.

Pulvermuller, F., Kujala, T., Shtyrov, Y., Simola, J., Tiitinen, H., Alku, P., et al. (2001). Memory traces for words as revealed by the mismatch negativity. *Neuroimage, 14*(3), 607-616.

Pulvermuller, F., & Shtyrov, Y. (2003). Automatic processing of grammar in the human brain as revealed by the mismatch negativity. *Neuroimage, 20*(1), 159-172.

Pulvermuller, F., & Shtyrov, Y. (2006). Language outside the focus of attention: the mismatch negativity as a tool for studying higher cognitive processes. *Prog Neurobiol, 79*(1), 49-71.

Reuter-Lorenz, P. A., & Cappell, K. A. (2008). Neurocognitive aging and the compensation hypothesis. *Current directions in psychological science, 17*(3), 177-182.

Ritchie, K., & Lovestone, S. (2002). The dementias. *Lancet, 360*(9347), 1759-1766.

Rogers, S. L., & Friedman, R. B. (2008). The underlying mechanisms of semantic memory loss in Alzheimer's disease and semantic dementia. *Neuropsychologia, 46*(1), 12-21.

Rosburg, T., Trautner, P., Korzyukov, O. A., Boutros, N. N., Schaller, C., Elger, C. E., et al. (2004). Short-term habituation of the intracranially recorded auditory evoked potentials P50 and N100. *Neurosci Lett, 372*(3), 245-249.

Rugg, M. D. (1985). The effects of semantic priming and word repetition on event-related potentials. *Psychophysiology, 22*(6), 642-647.

Salat, D. H., Buckner, R. L., Snyder, A. Z., Greve, D. N., Desikan, R. S., Busa, E., et al. (2004). Thinning of the cerebral cortex in aging. *Cereb Cortex, 14*(7), 721-730.

Scheltens, P., Fox, N., Barkhof, F., & De Carli, C. (2002). Structural magnetic resonance imaging in the practical assessment of dementia: beyond exclusion. *Lancet Neurol, 1*(1), 13-21.

Schiff, S., Valenti, P., Andrea, P., Lot, M., Bisiacchi, P., Gatta, A., et al. (2008). The effect of aging on auditory components of event-related brain potentials. *Clin Neurophysiol, 119*(8), 1795-1802.

Schliebs, R., & Arendt, T. (2006). The significance of the cholinergic system in the brain during aging and in Alzheimer's disease. *J Neural Transm, 113*(11), 1625-1644.

Schnyer, D. M., Allen, J. J., Kaszniak, A. W., & Forster, K. I. (1999). An event-related potential examination of masked and unmasked repetition priming in Alzheimer's disease: implications for theories of implicit memory. *Neuropsychology, 13*(3), 323-337.

Schwartz, T. J., Kutas, M., Butters, N., Paulsen, J. S., & Salmon, D. P. (1996). Electrophysiological insights into the nature of the semantic deficit in Alzheimer's disease. *Neuropsychologia, 34*(8), 827-841.

Sereno, S. C., & Rayner, K. (2003). Measuring word recognition in reading: eye movements and event-related potentials. *Trends Cogn Sci, 7*(11), 489-493.

Shtyrov, Y., Kimppa, L., Pulvermuller, F., & Kujala, T. (2011). Event-related potentials reflecting the frequency of unattended spoken words: a neuronal index of connection strength in lexical memory circuits? *Neuroimage, 55*(2), 658-668.

Shtyrov, Y., Kujala, T., & Pulvermuller, F. (2010). Interactions between language and attention systems: early automatic lexical processing? *J Cogn Neurosci, 22*(7), 1465-1478.

Shtyrov, Y., Pihko, E., & Pulvermuller, F. (2005). Determinants of dominance: is language laterality explained by physical or linguistic features of speech? *Neuroimage, 27*(1), 37-47.

Shtyrov, Y., & Pulvermuller, F. (2002). Neurophysiological evidence of memory traces for words in the human brain. *Neuroreport, 13*(4), 521-525.

Shtyrov, Y., & Pulvermuller, F. (2007). Early MEG Activation Dynamics in the Left Temporal and Inferior Frontal Cortex Reflect Semantic Context Integration. *J Cogn Neurosci, 19*(10), 1633-1642.

Shtyrov, Y., Pulvermuller, F., Naatanen, R., & Ilmoniemi, R. J. (2003). Grammar processing outside the focus of attention: an MEG study. *J Cogn Neurosci, 15*(8), 1195-1206.

Soros, P., Teismann, I. K., Manemann, E., & Lutkenhoner, B. (2009). Auditory temporal processing in healthy aging: a magnetoencephalographic study. *BMC Neurosci, 10*, 34.

Steffens, D. C., & Potter, G. G. (2008). Geriatric depression and cognitive impairment. *Psychol Med, 38*(2), 163-175.

Sussman, E. (2007). A new view on the MMN and attention debate: the role of context in processing auditory events. [review]. *J Psychophysiol, 21*(3-4), 164-175.

Sussman, E., & Winkler, I. (2001). Dynamic sensory updating in the auditory system. *Brain Res Cogn Brain Res, 12*(3), 431-439.

Sussman, E., Winkler, I., Huotilainen, M., Ritter, W., & Naatanen, R. (2002). Top-down effects on the initially stimulus-driven auditory organisation. *Cognitive Brain Research, 13*, 393-405.

Taulu, S., & Kajola, M. (2005). Presentation of electromagnetic multichannel data: The signal space separation method. *Journal of Applied Physics, 97*(12).

Taylor, J. R., & Olichney, J. M. (2007). From amnesia to dementia: ERP studies of memory and language. *Clin EEG Neurosci, 38*(1), 8-17.

Tendolkar, I., Schoenfeld, A., Golz, G., Fernandez, G., Kuhl, K. P., Ferszt, R., et al. (1999). Neural correlates of recognition memory with and without recollection in patients with Alzheimer's disease and healthy controls. *Neurosci Lett, 263*(1), 45-48.

Terry, R. D., Masliah, E., Salmon, D. P., Butters, N., DeTeresa, R., Hill, R., et al. (1991). Physical basis of cognitive alterations in Alzheimer's disease: synapse loss is the major correlate of cognitive impairment. *Ann Neurol, 30*(4), 572-580.

Thomas, C., vom Berg, I., Rupp, A., Seidl, U., Schroder, J., Roesch-Ely, D., et al. (2010). P50 gating deficit in Alzheimer dementia correlates to frontal neuropsychological function. *Neurobiol Aging, 31*(3), 416-424.

Ullman, M. T., Corkin, S., Coppola, M., Hickok, G., Crowden, J. H., Koroshetz, W. J., et al. (1997). A neural dissociation within language: Evidence that the mental dictinoary is just part of declarative memory, and that grammatical rules are processed by the procedural system. *Journal of cognitive neuroscience, 9*, 266-276.

Van Petten, C., Kutas, M., Kluender, R., Mitchiner, M., & McIsaac, H. (1991). Fractionating the word repetition effect with event-related potentials. *J Cogn Neurosci, 3*, 131-150.

Wijnen, V. J., van Boxtel, G. J., Eilander, H. J., & de Gelder, B. (2007). Mismatch negativity predicts recovery from the vegetative state. *Clin Neurophysiol, 118*(3), 597-605.

Williamson, S. J., & Kaufman, L. (1990). Theory of neuroelectric and neuromagnetic fields. In F. Grandori, M. Hoke & G. L. Romani (Eds.), *Auditory evoked magnetic fields and electric potentials* (pp. 1-39). Basel: Karger.

Wilson, R. S., Beckett, L. A., Barnes, L. L., Schneider, J. A., Bach, J., Evans, D. A., et al. (2002). Individual differences in rates of change in cognitive abilities of older persons. *Psychol Aging, 17*(2), 179-193.

Winkler, I., Karmos, G., & Naatanen, R. (1996). Adaptive modeling of the unattended acoustic environment reflected in the mismatch negativity event-related potential. *Brain Res, 742*(1-2), 239-252.

Woollams, A. M., Joanisse, M., & Patterson, K. (2009). Past-Tense Generation from Form Versus Meaning: Behavioural Data and Simulation Evidence. *Journal of memory and language, 61*(1), 55-76.

Woollams, A. M., Taylor, J. R., Karayanidis, F., & Henson, R. N. (2008). Event-related potentials associated with masked priming of test cues reveal multiple potential contributions to recognition memory. *J Cogn Neurosci, 20*(6), 1114-1129.

Worsley, K. J. (2005). An improved theoretical P value for SPMs based on discrete local maxima. *Neuroimage, 28*(4), 1056-1062.

Yokoyama, Y., Nakashima, K., Shimoyama, R., Urakami, K., & Takahashi, K. (1995). Distribution of event-related potentials in patients with dementia. *Electromyogr Clin Neurophysiol, 35*(7), 431-437.

Zouridakis, G., & Boutros, N. N. (1992). Stimulus parameter effects on the P50 evoked response. *Biol Psychiatry, 32*(9), 839-841.

Zwitserlood, P. (1989). The locus of the effects of sentential-semantic context in spoken-word processing. *Cognition, 32*(1), 25-64.

Appendix I – Active memory paradigm stimulus lists

Set A: Block 1

Auditory phrase	VISUAL WORD
Hair colour	BRUNETTE
Cleaning instrument	DUSTER
Hair colour	BRUNETTE
Type of bean	BUTTON
Cleaning instrument	DUSTER
Circus performer	CORN
Circus performer	CORN
Type of bean	BUTTON
Type of shoe	ALMOND
Child's toy	EAGLE
Child's toy	EAGLE
Item of sports equipment	RACQUET
Type of shoe	ALMOND
Edible root	PARSNIP
Item of sports equipment	RACQUET
Edible root	PARSNIP
Something to take to the beach	SUNCREAM
Reptile	IGUANA
Something to take to the beach	SUNCREAM
Electrical appliance	TOASTER
Reptile	IGUANA
Animal that hops	LITRE
Animal that hops	LITRE
Electrical appliance	TOASTER
Part of the eyes	EYEBALL
Dessert	WHITSUN
Dessert	WHITSUN
Dance	TANGO
Part of the eyes	EYEBALL
Mexican food	ENCHILADA
Dance	TANGO
Mexican food	ENCHILADA
Card game	SOLITAIRE
Cosmetic	NECK
Card game	SOLITAIRE

Set B: Block 1

Auditory phrase	VISUAL WORD
Bank holiday	WHITSUN
Two wheeled vehicle	SCOOTER
Bank holiday	WHITSUN
Mexican food	ELM
Two wheeled vehicle	SCOOTER
Edible root	JAZZ
Edible root	JAZZ
Mexican food	ELM
Card game	CAPTAIN
Kitchen utensil	BRACELET
Kitchen utensil	BRACELET
Fruit with green flesh	KIWI
Card game	CAPTAIN
Circus performer	JUGGLER
Fruit with green flesh	KIWI
Circus performer	JUGGLER
Red vegetable	RADISH
Dessert	ICECREAM
Red vegetable	RADISH
Flu symptom	SNEEZING
Dessert	ICECREAM
Type of cheese	GRAPEFUIT
Type of cheese	GRAPEFUIT
Flu symptom	SNEEZING
Astrological sign	AQUARIUS
Reptile	CHISEL
Reptile	CHISEL
Breed of housecat	TABBY
Astrological sign	AQUARIUS
Type of bean	CHICKPEA
Breed of housecat	TABBY
Type of bean	CHICKPEA
Type of shoe	SANDAL
Insect	BATTERY
Type of shoe	SANDAL

Red vegetable	CEMENT
Cosmetic	NECK
Type of confectionary	LICORICE
Type of confectionary	LICORICE
Red vegetable	CEMENT
Kitchen utensil	SPATULA
Type of bread	PITTA
Type of bread	PITTA
Type of bear	KOALA
Kitchen utensil	SPATULA
Fruit with green flesh	WATER
Type of bear	KOALA
Fruit with green flesh	WATER
Type of cheese	MOZZARELLA
Bank holiday	RUSSIAN
Type of cheese	MOZZARELLA
Fruit with a stone	VOLVO
Bank holiday	RUSSIAN
Breed of housecat	CHICKPEA
Breed of housecat	CHICKPEA
Fruit with a stone	VOLVO
Two wheeled vehicle	TRIPOD
Winter sport	BOBSLEIGH
Winter sport	BOBSLEIGH
Astrological sign	TENT
Two wheeled vehicle	TRIPOD
Insect	LADYBIRD
Astrological sign	TENT
Insect	LADYBIRD
A salty food	YO-YO
American coin	BRAIN
A salty food	YO-YO
Flu symptom	COW
American coin	BRAIN
Scuba diving equipment	BRISTOL
Scuba diving equipment	BRISTOL
Flu symptom	COW

Something to take to the beach	WARDROBE
Insect	BATTERY
A salty food	CRISPS
A salty food	CRISPS
Something to take to the beach	WARDROBE
Child's toy	YO-YO
American coin	DIME
American coin	DIME
Scuba diving equipment	SNORKEL
Child's toy	YO-YO
Item of sports equipment	STEEL
Scuba diving equipment	SNORKEL
Item of sports equipment	STEEL
Animal that hops	GRASSHOPPER
Hair colour	CHANCELLOR
Animal that hops	GRASSHOPPER
Winter sport	DUSTER
Hair colour	CHANCELLOR
Dance	CUCUMBER
Dance	CUCUMBER
Winter sport	DUSTER
Cleaning instrument	TANGO
Fruit with a stone	NECTARINE
Fruit with a stone	NECTARINE
Part of the eyes	COAL
Cleaning instrument	TANGO
Cosmetic	EYESHADOW
Part of the eyes	COAL
Cosmetic	EYESHADOW
Type of confectionary	LEAF
Type of bread	TONNE
Type of confectionary	LEAF
Electrical appliance	MOZZARELLA
Type of bread	TONNE
Type of bear	TROUSERS
Type of bear	TROUSERS
Electrical appliance	MOZZARELLA

Set A: Block 2

Auditory phrase	VISUAL WORD
Planet	SATURN
Poison	MOZART
Planet	SATURN
Part of a door	BOSTON
Poison	MOZART
Type of alcoholic spirit	WHISKEY
Type of alcoholic spirit	WHISKEY
Part of a door	BOSTON
Carpenter's tool	CHISEL
Snake	COWBOY
Snake	COWBOY
Fast food	DAWN
Carpenter's tool	CHISEL
Baby animal	CUB
Fast food	DAWN
Baby animal	CUB
Green vegetable	TRIANGLE
American car manufacturer	CHRYSLER
Green vegetable	TRIANGLE
Water sport	SANDAL
American car manufacturer	CHRYSLER
Jewellery	BRACELET
Jewellery	BRACELET
Water sport	SANDAL
Mathematical operation	ETHIOPIA
Part of the hand	COBRA
Part of the hand	COBRA
Electrical tool	SNORKEL
Mathematical operation	ETHIOPIA
Surgical tool	SCALPEL
Electrical tool	SNORKEL
Surgical tool	SCALPEL
Medicine	PENICILLIN
Religious item	ROSARY
Medicine	PENICILLIN
Breed of dog	POODLE
Religious item	ROSARY

Set B: Block 2

Auditory phrase	VISUAL WORD
Photographic equipment	TRIPOD
Surgical tool	MOSQUE
Photographic equipment	TRIPOD
Alcoholic mixed drink	PITTA
Surgical tool	MOSQUE
Mathematical operation	SUBTRACT
Mathematical operation	SUBTRACT
Alcoholic mixed drink	PITTA
Icecream flavour	VANILLA
Mountain range	FORK
Mountain range	FORK
Something to put in a salad	RUGBY
Icecream flavour	VANILLA
Herb	THYME
Something to put in a salad	RUGBY
Herb	THYME
Jewellery	INDIA
Type of wood	CEDAR
Jewellery	INDIA
Punctuation mark	SUNCREAM
Type of wood	CEDAR
Green vegetable	SPINACH
Green vegetable	SPINACH
Punctuation mark	SUNCREAM
Type of alcoholic spirit	HURRICANE
Person in a wedding ceremony	SATURN
Person in a wedding ceremony	SATURN
Religious item	THEFT
Type of alcoholic spirit	HURRICANE
Poison	CYANIDE
Religious item	THEFT
Poison	CYANIDE
Type of gun	REVOLVER
Electrical tool	SANDER
Type of gun	REVOLVER
Flower	DAFFODIL
Electrical tool	SANDER

Mountain range	ANDES
Mountain range	ANDES
Breed of dog	POODLE
Flower	WHALE
Type of exercise	NEWCASTLE
Type of exercise	NEWCASTLE
Type of wood	GRASSHOPPER
Flower	WHALE
Name of a finger	INDEX
Type of wood	GRASSHOPPER
Name of a finger	INDEX
Musical wind instrument	CEDAR
Herb	CHICKEN
Musical wind instrument	CEDAR
Kind of juice	GRAPEFUIT
Herb	CHICKEN
Photographic equipment	BURGER
Photographic equipment	BURGER
Kind of juice	GRAPEFUIT
Type of gun	SEVENTEEN
Something to put in a salad	CUCUMBER
Something to put in a salad	CUCUMBER
Icecream flavour	LUKE
Type of gun	SEVENTEEN
Spice	BOTANY
Icecream flavour	LUKE
Spice	BOTANY
Person in a wedding ceremony	BRIDESMAID
Alcoholic mixed drink	MARTINI
Person in a wedding ceremony	BRIDESMAID
Shellfish	OYSTER
Alcoholic mixed drink	MARTINI
Punctuation mark	COMMA
Punctuation mark	COMMA
Shellfish	OYSTER

Snake	COBRA
Snake	COBRA
Flower	DAFFODIL
Breed of dog	SWORD
Shellfish	DICKENS
Shellfish	DICKENS
American car manufacturer	PRINCE
Breed of dog	SWORD
Spice	NUTMEG
American car manufacturer	PRINCE
Spice	NUTMEG
Kind of juice	CUB
Baby animal	ROSARY
Kind of juice	CUB
Musical wind instrument	OBOE
Baby animal	ROSARY
Planet	TILE
Planet	TILE
Musical wind instrument	OBOE
Medicine	SIGHT
Fast food	BURGER
Fast food	BURGER
Carpenter's tool	PIZZA
Medicine	SIGHT
Name of a finger	BUS
Carpenter's tool	PIZZA
Name of a finger	BUS
Part of the hand	KNUCKLE
Part of a door	HINGE
Part of the hand	KNUCKLE
Type of exercise	YOGA
Part of a door	HINGE
Water sport	SURFING
Water sport	SURFING
Type of exercise	YOGA

Set A: Block 3

Auditory phrase	VISUAL WORD
Foreign currency	ZIP
Precious stone	JUGGLER
Foreign currency	ZIP
Children's party food	SUBTRACT
Precious stone	JUGGLER
Dairy product	YOGHURT
Dairy product	YOGHURT
Children's party food	SUBTRACT
Unit of weight	TONNE
Floor covering	TILE
Floor covering	TILE
Former U.S. president	MADRID
Unit of weight	TONNE
Item of winter clothing	CRISPS
Former U.S. president	MADRID
Item of winter clothing	CRISPS
Something worn on the foot	SOCK
Something to sweeten food	SYRUP
Something worn on the foot	SOCK
Tree	ELM
Something to sweeten food	SYRUP
Japanese car manufacturer	VANILLA
Japanese car manufacturer	VANILLA
Tree	ELM
Country in Africa	PENCIL
Rodent	SQUIRREL
Rodent	SQUIRREL
Part of a boat	GLASGOW
Country in Africa	PENCIL
Entertainer	COMEDIAN
Part of a boat	GLASGOW
Entertainer	COMEDIAN
Unit of liquid measure	SCARF
Breakfast food	CEREAL
Unit of liquid measure	SCARF
Type of wildcat	ANGER
Breakfast food	CEREAL

Set B: Block 3

Auditory phrase	VISUAL WORD
Biblical name	PERU
Tree	CHESS
Biblical name	PERU
Italian food	COMMA
Tree	CHESS
Part of a boat	RUDDER
Part of a boat	RUDDER
Italian food	COMMA
Edible nut	ALMOND
European car manufacturer	VOLVO
European car manufacturer	VOLVO
Pizza topping	AUNT
Edible nut	ALMOND
Animal to ride on	BOMB
Pizza topping	AUNT
Animal to ride on	BOMB
Type of wildcat	LEOPARD
Vehicle	MOTORCYCLE
Type of wildcat	LEOPARD
Precious stone	EMERALD
Vehicle	MOTORCYCLE
Entertainer	CEREAL
Entertainer	CEREAL
Precious stone	EMERALD
Breakfast food	CHEEKS
Science	BOTANY
Science	BOTANY
Dairy product	VAT
Breakfast food	CHEEKS
Japanese car manufacturer	NISSAN
Dairy product	VAT
Japanese car manufacturer	NISSAN
Weather phenomenon	LICORICE
Country in Africa	ETHIOPIA
Weather phenomenon	LICORICE
Something worn on the foot	MARTINI
Country in Africa	ETHIOPIA

Biblical name	ABRAHAM
Biblical name	ABRAHAM
Type of wildcat	ANGER
Garden tool	HOCKEY
Part of a bicycle	PEDAL
Part of a bicycle	PEDAL
Religious building	MOSQUE
Garden tool	HOCKEY
Type of hat	YEN
Religious building	MOSQUE
Type of hat	YEN
Science	SPINACH
Weather phenomenon	HURRICANE
Science	SPINACH
Covering for windows	BLINDS
Weather phenomenon	HURRICANE
Large river	AMAZON
Large river	AMAZON
Covering for windows	BLINDS
Animal to ride on	DONKEY
European car manufacturer	KNEE
European car manufacturer	KNEE
Natural earth formation	YACHT
Animal to ride on	DONKEY
Clothes fastener	BIOLOGY
Natural earth formation	YACHT
Clothes fastener	BIOLOGY
Italian food	PIZZA
Vehicle	ITALY
Italian food	PIZZA
Pizza topping	MUSHROOM
Vehicle	ITALY
Edible nut	RUDDER
Edible nut	RUDDER
Pizza topping	MUSHROOM

Foreign currency	YEN
Foreign currency	YEN
Something worn on the foot	MARTINI
Religious building	IGUANA
Natural earth formation	VOLCANO
Natural earth formation	VOLCANO
Garden tool	SPADE
Religious building	IGUANA
Covering for windows	HELICOPTER
Garden tool	SPADE
Covering for windows	HELICOPTER
Rodent	BRIDESMAID
Unit of liquid measure	LITRE
Rodent	BRIDESMAID
Type of hat	COWBOY
Unit of liquid measure	LITRE
Clothes fastener	ZIP
Clothes fastener	ZIP
Type of hat	COWBOY
Item of winter clothing	SCARF
Floor covering	SYRUP
Floor covering	SYRUP
Part of a bicycle	ANDES
Item of winter clothing	SCARF
Large river	EYEBALL
Part of a bicycle	ANDES
Large river	EYEBALL
Children's party food	JELLY
Something to sweeten food	KOALA
Children's party food	JELLY
Former U.S. president	ROOSEVELT
Something to sweeten food	KOALA
Unit of weight	CHRYSLER
Unit of weight	CHRYSLER
Former U.S. president	ROOSEVELT

Set A: Block 4

Auditory phrase	VISUAL WORD
Musical instrument with strings	YOGA
European city	BUNGALOW
Musical instrument with strings	YOGA
Human dwelling	LEOPARD
European city	BUNGALOW
Type of grain	NYLON
Type of grain	NYLON
Human dwelling	LEOPARD
Part of a living room	THYME
Farm equipment	TRACTOR
Farm equipment	TRACTOR
Boat	NUTMEG
Part of a living room	THYME
Welsh town	SWANSEA
Boat	NUTMEG
Welsh town	SWANSEA
Writing instrument	MOTORCYCLE
Team sport	SANDER
Writing instrument	MOTORCYCLE
Part of the foot	ATLANTIC
Team sport	SANDER
American city	KIWI
American city	KIWI
Part of the foot	ATLANTIC
Member of the clergy	VICAR
Camping equipment	DIME
Camping equipment	DIME
Building material	METRE
Member of the clergy	VICAR
Article of bedding	BLANKET
Building material	METRE
Article of bedding	BLANKET
Game	CHESS
Baking ingredient	FLOUR
Game	CHESS
Scientific instrument	MICROSCOPE
Baking ingredient	FLOUR

Set B: Block 4

Auditory phrase	VISUAL WORD
Animal found in a zoo	ABRAHAM
Eating utensil	BLANKET
Animal found in a zoo	ABRAHAM
Farm equipment	SPATULA
Eating utensil	BLANKET
Type of music	TRACTOR
Type of music	TRACTOR
Farm equipment	SPATULA
Part of a bedroom	ENCHILADA
Human dwelling	BUNGALOW
Human dwelling	BUNGALOW
Illegal drug	PARSNIP
Part of a bedroom	ENCHILADA
Building material	CEMENT
Illegal drug	PARSNIP
Building material	CEMENT
Vehicle that flies	SOCK
Scientific instrument	RACQUET
Vehicle that flies	SOCK
Game	TOBACCO
Scientific instrument	RACQUET
Painter	PEDAL
Painter	PEDAL
Game	TOBACCO
Unit of length	METRE
Article of bedding	RABBIT
Article of bedding	RABBIT
Welsh town	INDEX
Unit of length	METRE
Camping equipment	TENT
Welsh town	INDEX
Camping equipment	TENT
Part of the foot	TOE
Academic discipline	BIOLOGY
Part of the foot	TOE
Team sport	HOCKEY
Academic discipline	BIOLOGY

Part of a bedroom	WARDROBE
Part of a bedroom	WARDROBE
Scientific instrument	MICROSCOPE
Country in South America	PERU
Fabric	SALMON
Fabric	SALMON
Item used in rainy weather	ROOSEVELT
Country in South America	PERU
Vehicle that flies	HELICOPTER
Item used in rainy weather	ROOSEVELT
Vehicle that flies	HELICOPTER
Marine mammal	HINGE
Part of an aeroplane	COCKPIT
Marine mammal	HINGE
Sticky substance	GLUE
Part of an aeroplane	COCKPIT
Animal found in a zoo	MONKEY
Animal found in a zoo	MONKEY
Sticky substance	GLUE
Unit of length	SNEEZING
Famous writer	DICKENS
Famous writer	DICKENS
Geometrical shape	WINTER
Unit of length	SNEEZING
Painter	PICASSO
Geometrical shape	WINTER
Painter	PICASSO
Illegal drug	HEROIN
Eating utensil	FORK
Illegal drug	HEROIN
Academic discipline	WALL
Eating utensil	FORK
Type of music	JAZZ
Type of music	JAZZ
Academic discipline	WALL

Part of a living room	SOFA
Part of a living room	SOFA
Team sport	HOCKEY
Geometrical shape	TRIANGLE
Famous writer	HOUR
Famous writer	HOUR
Sticky substance	GOLF
Geometrical shape	TRIANGLE
Writing instrument	PENCIL
Sticky substance	GOLF
Writing instrument	PENCIL
Part of an aeroplane	COMEDIAN
Marine mammal	WHALE
Part of an aeroplane	COMEDIAN
Item used in rainy weather	UMBRELLA
Marine mammal	WHALE
Musical instrument with strings	VIOLIN
Musical instrument with strings	VIOLIN
Item used in rainy weather	UMBRELLA
Member of the clergy	PAPER
Fabric	NYLON
Fabric	NYLON
Country in South America	SWANSEA
Member of the clergy	PAPER
American city	BOSTON
Country in South America	SWANSEA
American city	BOSTON
Boat	YACHT
European city	MADRID
Boat	YACHT
Baking ingredient	CANCER
European city	MADRID
Type of grain	CORN
Type of grain	CORN
Baking ingredient	CANCER

Set A: Block 5

Auditory phrase	VISUAL WORD
Pet	RABBIT
Four-footed animal	RECEIVER
Pet	RABBIT
Continent	AQUARIUS
Four-footed animal	RECEIVER
Joint of the body	RADISH
Joint of the body	RADISH
Continent	AQUARIUS
Citrus fruit	LEMON
Ball game	RUGBY
Ball game	RUGBY
Part of a shirt	ASIA
Citrus fruit	LEMON
Crime	THEFT
Part of a shirt	ASIA
Crime	THEFT
Part of a day	EYESHADOW
Branch of the Armed Services	NAVY
Part of a day	EYESHADOW
Part of a face	CHEEKS
Branch of the Armed Services	NAVY
Part of a tree	LEAF
Part of a tree	LEAF
Part of a face	CHEEKS
Religion	CHRISTIANITY
Meat	DAFFODIL
Meat	DAFFODIL
Bird	REVOLVER
Religion	CHRISTIANITY
Composer	SCOOTER
Bird	REVOLVER
Composer	SCOOTER
Male relative	SURFING
Number	SUNDAY
Male relative	SURFING
Fish	OBOE
Number	SUNDAY

Set B: Block 5

Auditory phrase	VISUAL WORD
Fish	SALMON
Weapon	TOASTER
Fish	SALMON
Instrument of war	SKIRT
Weapon	TOASTER
Religion	POODLE
Religion	POODLE
Instrument of war	SKIRT
Bird	EAGLE
Part of a day	DAWN
Part of a day	DAWN
Part of a tree	RIVER
Bird	EAGLE
Number	SEVENTEEN
Part of a tree	RIVER
Number	SEVENTEEN
Ball game	WHISKEY
Meat	CHICKEN
Ball game	WHISKEY
Part of a telephone	RECEIVER
Meat	CHICKEN
Part of a shirt	BUTTON
Part of a shirt	BUTTON
Part of a telephone	RECEIVER
Joint of the body	KNEE
Branch of the Armed Services	SQUIRREL
Branch of the Armed Services	SQUIRREL
Citrus fruit	PENICILLIN
Joint of the body	KNEE
Chemical element	FLOUR
Citrus fruit	PENICILLIN
Chemical element	FLOUR
Item used by smokers	LARGE
Crime	PINK
Item used by smokers	LARGE
Pet	YOGHURT
Crime	PINK

City in South West England	TABBY
City in South West England	TABBY
Fish	OBOE
Instrument of war	BOMB
Ocean	KNUCKLE
Ocean	KNUCKLE
City in the North of England	DRIVING
Instrument of war	BOMB
Part of a telephone	UMBRELLA
City in the North of England	DRIVING
Part of a telephone	UMBRELLA
Taste	VIOLIN
Item used by smokers	TOBACCO
Taste	VIOLIN
Part of a bathroom	BATH
Item used by smokers	TOBACCO
Item of male clothing	TROUSERS
Item of male clothing	TROUSERS
Part of a bathroom	BATH
Tax	VAT
Female relative	AUNT
Female relative	AUNT
Weapon	SWORD
Tax	VAT
Meal	NOVEMBER
Weapon	SWORD
Meal	NOVEMBER
Part of a watch	BATTERY
Chemical element	HYDROGEN
Part of a watch	BATTERY
Part of a kitchen	DEMOCRACY
Chemical element	HYDROGEN
Item of female clothing	SKIRT
Item of female clothing	SKIRT
Part of a kitchen	DEMOCRACY

Female relative	GLUE
Female relative	GLUE
Pet	YOGHURT
Continent	ASIA
Item of male clothing	PICASSO
Item of male clothing	PICASSO
Part of a bathroom	SOLITAIRE
Continent	ASIA
Part of a face	BATH
Part of a bathroom	SOLITAIRE
Part of a face	BATH
Tax	CHRISTIANITY
Male relative	GRANDFATHER
Tax	CHRISTIANITY
City in the North of England	NEWCASTLE
Male relative	GRANDFATHER
Ocean	ATLANTIC
Ocean	ATLANTIC
City in the North of England	NEWCASTLE
Taste	BITTER
City in South West England	BRISTOL
City in South West England	BRISTOL
Four-footed animal	COW
Taste	BITTER
Item of female clothing	SCALPEL
Four-footed animal	COW
Item of female clothing	SCALPEL
Part of a kitchen	OVEN
Composer	MOZART
Part of a kitchen	OVEN
Part of a watch	TEACHER
Composer	MOZART
Meal	SUPPER
Meal	SUPPER
Part of a watch	TEACHER

Set A: Block 6

Auditory phrase	VISUAL WORD
Organ of the body	OVEN
Country in Europe	SPADE
Organ of the body	OVEN
Type of fuel	COAL
Country in Europe	SPADE
Country in Asia	INDIA
Country in Asia	INDIA
Type of fuel	COAL
Direction on a compass	OXFORD
Form of public transport	BUS
Form of public transport	BUS
Item of office supplies	PAPER
Direction on a compass	OXFORD
Season of the year	JELLY
Item of office supplies	PAPER
Season of the year	JELLY
Position in government	CHANCELLOR
One of the five senses	SIGHT
Position in government	CHANCELLOR
Type of license	GRANDFATHER
One of the five senses	SIGHT
Part of a car	SOFA
Part of a car	SOFA
Type of license	GRANDFATHER
Foreign language	ICECREAM
Type of reading material	MAGAZINE
Type of reading material	MAGAZINE
Part of the human body	NISSAN
Foreign language	ICECREAM
Disease	CANCER
Part of the human body	NISSAN
Disease	CANCER
Unit of time	HOUR
Individual sport	GOLF
Unit of time	HOUR
Size of T-shirt	LARGE
Individual sport	GOLF

Set B: Block 6

Auditory phrase	VISUAL WORD
Type of reading material	BLINDS
Type of fuel	LADYBIRD
Type of reading material	BLINDS
Country in Europe	ITALY
Type of fuel	LADYBIRD
Part of a car	ENGINE
Part of a car	ENGINE
Country in Europe	ITALY
Item of office supplies	COCKPIT
Foreign language	RUSSIAN
Foreign language	RUSSIAN
Direction on a compass	EAST
Item of office supplies	COCKPIT
One of the five senses	VICAR
Direction on a compass	EAST
One of the five senses	VICAR
Emotion	ANGER
Season of the year	WINTER
Emotion	ANGER
Male member of royalty	BRUNETTE
Season of the year	WINTER
Country in Asia	DONKEY
Country in Asia	DONKEY
Male member of royalty	BRUNETTE
Form of public transport	HEROIN
Organ of the body	BRAIN
Organ of the body	BRAIN
Military title	QUEEN
Form of public transport	HEROIN
Scottish city	GLASGOW
Military title	QUEEN
Scottish city	GLASGOW
Part of a building	WALL
One of Jesus' disciples	LUKE
Part of a building	WALL
Non-alcoholic beverage	WATER
One of Jesus' disciples	LUKE

Profession	TEACHER
Profession	TEACHER
Size of T-shirt	LARGE
Day of the week	MILE
Metal	STEEL
Metal	STEEL
Colour	PINK
Day of the week	MILE
Form of government	TOE
Colour	PINK
Form of government	TOE
One of Jesus' disciples	NECTARINE
Emotion	CYANIDE
One of Jesus' disciples	NECTARINE
Military title	CAPTAIN
Emotion	CYANIDE
Unit of distance	VOLCANO
Unit of distance	VOLCANO
Military title	CAPTAIN
Female member of royalty	QUEEN
Part of a building	ENGINE
Part of a building	ENGINE
British university	BITTER
Female member of royalty	QUEEN
Non-alcoholic beverage	EAST
British university	BITTER
Non-alcoholic beverage	EAST
Male member of royalty	PRINCE
Month of the year	EMERALD
Male member of royalty	PRINCE
Body of water	RIVER
Month of the year	EMERALD
Scottish city	SUPPER
Scottish city	SUPPER
Body of water	RIVER

Day of the week	SUNDAY
Day of the week	SUNDAY
Non-alcoholic beverage	WATER
Profession	HYDROGEN
Form of government	DEMOCRACY
Form of government	DEMOCRACY
Unit of distance	MILE
Profession	HYDROGEN
Metal	MUSHROOM
Unit of distance	MILE
Metal	MUSHROOM
Individual sport	MONKEY
Position in government	MICROSCOPE
Individual sport	MONKEY
Part of the human body	NECK
Position in government	MICROSCOPE
Colour	AMAZON
Colour	AMAZON
Part of the human body	NECK
British university	OXFORD
Unit of time	BOBSLEIGH
Unit of time	BOBSLEIGH
Female member of royalty	LEMON
British university	OXFORD
Size of T-shirt	MAGAZINE
Female member of royalty	LEMON
Size of T-shirt	MAGAZINE
Type of license	DRIVING
Body of water	OYSTER
Type of license	DRIVING
Month of the year	NOVEMBER
Body of water	OYSTER
Disease	NAVY
Disease	NAVY
Month of the year	NOVEMBER