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Implicit Memory

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Contents

I. Introduction: Implicit versus Explicit memory

This chapter is concerned with imaging studies of implicit memory. A subsequent chapter is concerned with explicit memory (Henson, this volume). These terms were introduced by Graf and Schacter (1985), and are used in the present context to refer to the phenomenological experience of whether memory retrieval is accompanied by conscious awareness of the past (explicit memory) or is not (implicit memory). This distinction is based primarily on studies of the amnesic syndrome, which suggest that amnesic patients can show effects of prior experience in their behaviour, even when they are not apparently aware of the prior experience. For example, many studies have shown that, when asked to identify a fragmented word, amnesic patients are more likely to identify such words if they have seen them previously in a "study" phase (Warrington & Weiskrantz, 1974). This "priming" effect is typically as large as that seen in healthy controls. However, when the patients are given the same type of word fragments, but this time asked to use them as cues to recall the corresponding word from a study phase, they are much worse than controls (Graf et al., 1984). Thus, the patients are said to have intact implicit memory but impaired explicit memory. The dissociation between implicit and explicit memory is further supported by functional dissociations in healthy individuals, such as differential effects of study processing (Jacoby & Dallas, 1981) and retention interval (Tulving et al., 1982).

Implicit memory is normally associated with "indirect" memory tasks (such as the word identification task described above), in which no reference is made to the previous experience (Richardson-Klavehn & Bjork, 1988). This is in contrast with "direct" memory tasks (such as recall and recognition), which refer participants to previous experiences. However, it is important to distinguish between the type of memory retrieval (implicit/explicit), its hypothetical underlying neural basis, and the type of tests used to measure memory (Schacter & Tulving, 1994). For example, even though an indirect test does not refer participants to a previous experience, participants may voluntarily, or involuntarily, recollect that experience. Conversely, unconscious forms of memory may influence performance on a direct memory task. In other words, direct or indirect memory tests are not necessarily "pure", in the sense that performance on either could involve a mixture of both implicit and explicit memory. That is, people may consciously recall some aspects of a prior episode, but not other aspects that nonetheless affect their behaviour. As a consequence, considerable effort has been devoted to developing methods that dissociate implicit and explicit contributions to memory tasks (Hayman & Tulving, 1989; Jacoby et al., 1993; Richardson-Klavehn & Gardiner, 1995; Schacter et al., 1989). Few imaging studies to date have achieved this dissociation however. Thus, it must be kept in mind that the brain activations discussed in the present (and subsequent) chapter may reflect contributions of implicit, explicit, or both types of memory.

The present chapter is confined to imaging studies directed at one example of implicit memory, "repetition priming". Likewise, the subsequent chapter (Henson, this volume) is confined to one example of explicit memory, "recognition memory". The reason for restricting interest to these two examples is that the paradigms used to investigate them are similar, facilitating their comparison. In both cases, the basic contrast is between repeated and initial presentations of stimuli within the experimental context. In the context of priming, these conditions are often called "primed" and "unprimed" respectively; in the context of recognition memory, the conditions are often called "old" and "new" respectively. More generally, the two conditions will be termed "repetition" and "control" conditions, and the subtraction of the

PET/fMRI data for repetition conditions from those for control conditions will be termed the "repetition effect".

In some cases, the control condition consists of the initial presentations of the same stimulus, perhaps in a separate "study" phase; in other cases, the control condition consists of different stimuli that were not presented previously. In some cases, the stimuli in the repetition condition are not repeated exactly; instead the "repetition" pertains to a common referent of the stimulus. For example, the primed stimulus in a priming paradigm (the "target") may only be semantically related to a previous stimulus (the "prime"); or the words in a recognition memory test may be studied visually, but tested auditorily. The important difference between the two paradigms is whether the test instructions are indirect (e.g, "does this stimulus depict an animate object?", with the behavioural measure of priming being a shorter response time) or direct (e.g, "did you see this stimulus in the study phase?", with the behavioural measure of recognition being response accuracy).

One potential generalisation that has emerged from imaging studies of these two paradigms is that priming is associated with a reduced haemodynamic response for repetition versus control conditions (a negative repetition effect, or "repetition suppression"), whereas recognition memory is associated with an increased response for the repetition condition (a positive repetition effect, or "repetition enhancement"). One purpose of the present chapter however is to argue that this generalisation is likely to be too simplistic (see Section II).

Given the plethora of recent imaging studies on memory, even when restricted to repetition priming and recognition memory, the reviews in both chapters must also be selective. Thus both chapters concentrate on studies performed at the Wellcome Department of Imaging Neuroscience (for more comprehensive reviews of priming, see Henson, submitted; Schacter & Buckner, 1998).

II. Introduction: Repetition Priming

This chapter concentrates on PET and fMRI studies of priming. As stated above, repetition priming has been associated with a reduction in the haemodynamic response. Furthermore, this repetition suppression is normally restricted to regions that are generally responsive to the stimuli used (e.g, regions activated by repeated and control stimuli versus a low-level baseline such as fixation, Schacter & Buckner, 1998). A simple interpretation of this finding is that the suppression reflects facilitated processing of a repeated stimulus (the target), owing performance of the same processes in the recent past (on the prime) – the "hot-tubes" or "greased tracks" metaphors.

A second observation is that repetition effects are often seen in multiple brain regions, suggesting that several stages in the processing pathway between stimulus and response can be facilitated (one or all of which may contribute to the behavioural measure of priming). Indeed, the amount of behavioural priming may depend on the degree of overlap between the pathways used for prime and target – the "component process" view of priming (Henson, submitted; Witherspoon & Moscovitch, 1989). A third observation is that repetition effects are not seen in all regions associated with processing stimuli in the task. For example, repetition effects are not normally seen in early visual regions or late motor regions in visual-motor priming paradigms. This suggests that not all component processes between stimulus and response are facilitated by

repetition. The computational properties of a process that determine whether it can be significantly facilitated by repetition is an important though, as yet, unresolved question.[1]

The next section focuses on examples of face priming. One important conclusion resulting from these studies is that priming may also be associated with a repetition increase (repetition enhancement) under some conditions.

III. Suppression vs. Enhancement: Face Priming

A series of three experiments have explored effects of face repetition during indirect tasks, using various manipulations of the face images and/or face familiarity. The focus of these experiments has been on the lateral midfusiform, a region widely implicated in face processing (Kanwisher et al., 1997). As can be seen in Figure 1, the pattern of repetition effects in this region across the three studies is complex, and appears to contain discrepancies (e.g, the opposite interactions between face familiarity and repetition in the George et al., 1999, and Henson et al., 2000, studies). However, there are important differences between the stimuli used, and the complex pattern can be explained by a combination of two assumptions (Henson, submitted).

The first assumption is that, when the same process occurs on initial and repeated presentations of a stimulus, a region subserving that process will show repetition suppression (as in Section II above). However, when priming causes a process to occur on repeated presentations that did not occur on initial presentations, the region will show repetition enhancement. This assumption applies, in principle, to any form of priming. The second assumption, which is specific to face priming studies, is that the particular processes subserved by the right lateral midfusiform include both face perception (i.e, discrimination of faces from non-face visual objects) and face recognition (i.e, discrimination between familiar and unfamiliar faces).

Participants in the PET study of Dolan et al. (1997) passively viewed binarized images of either unfamiliar faces or objects, which were difficult to perceive as such on their initial presentation. When these degraded images were repeated following intervening presentation of an intact, greyscale version of each image (Figure 1A), a greater number were reported to give a clear percept (though not when irrelevant images intervened, indicating stimulus-specific priming, rather than general practice effect). Greater responses to primed than unprimed face images was observed in a right midfusiform region (+44 –38 –28). This repetition enhancement can be attributed to a new process of face perception that occurred more often for repeated than initial image presentations.

Participants in the blocked fMRI study of George et al. (1999) viewed two-tone images of either famous or unfamiliar faces (Figure 1B), monitoring for a rare target stimulus (not of interest). For the “positive images”, the shading provided by the light/dark tones was sufficient to identify the famous faces. For the “negative images”, the contrast polarity of the tones was reversed, producing faces that were difficult to identify (only ~20% of famous face negatives were identified). Identification of famous negatives was made easier (~45% identified) when they were primed by positive images of the same face. Greater bilateral midfusiform responses (e.g, +46 –54 –12) were seen for blocks of famous negatives that were preceded by positive versions (primed) than for blocks of famous negatives that were not (unprimed). In contrast, these regions exhibited decreased responses to blocks of unfamiliar negatives that were preceded by positive versions, relative to blocks of unfamiliar negatives that were not.

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[1] A “process” in the current context is assumed to be a mapping or transformation between two representations, at least one of which is stimulus-specific.

An important difference between the George et al. (1999) and Dolan et al. (1997) studies is that the two-tone images of George et al. were perceived as faces, unlike (initial presentations of) the binarized images of Dolan et al. Thus in the George et al. study, face perception occurred for both primed and unprimed face negatives, and the repetition of this process explains the repetition suppression for primed unfamiliar negatives. For the famous negatives however, additional face recognition was more likely for primed than unprimed blocks. Assuming that the fusiform response increase owing to face recognition was sufficient to outweigh the decrease owing to repeated face perception, the repetition enhancement for famous negatives is consistent with the present hypothesis.

Participants in the third study of Henson et al. (2000) again performed an indirect target-monitoring task, this time while viewing intact images of famous and unfamiliar faces, each of which was presented twice in a randomised event-related fMRI design (Figure 1C). The right midfusiform (+45 –57 –24) evidenced an interaction between face familiarity and repetition, with repetition suppression for famous faces, but repetition enhancement for unfamiliar faces.

An important difference between the famous faces of George et al. (1999) and Henson et al. (2000) is that the intact famous faces of Henson et al. could be recognised on initial presentations, unlike the unprimed famous negatives of George et al. Thus face recognition (and perception) occurred in the Henson et al. study for both initial and repeated presentations of famous faces, explaining the associated fusiform repetition suppression. To explain the repetition enhancement for unfamiliar faces, Henson et al. (2000) assumed that a single presentation of an intact unfamiliar face was sufficient to form a new, structural representation of that face, such that it can be recognised (as familiar) when repeated.[2] This additional process of face recognition on repeated but not initial presentations of unfamiliar faces can then explain the repetition enhancement.

The assumption that initial presentations of unfamiliar stimuli can, under some conditions, form a new structural representation is consistent with the Perceptual Representation System hypothesis of Schacter (1990). Indeed, this assumption also allows the present hypothesis to explain the repetition effects observed in a PET study of Schacter et al. (1995). This study used 2D drawings of abstract (unfamiliar) objects, which either could or could not exist in 3D ("possible" or "impossible" objects respectively). Behavioural experiments have shown that only the possible objects can be primed (Cooper et al., 1992), leading to the hypothesis that new structural representations are only formed in the PRS for objects that are structurally coherent. Consistent with this, Schacter et al. (1995) only found a fusiform repetition effects for possible objects. Importantly, this repetition effect was a repetition enhancement. This pattern can be explained if, in addition to perception (of a 3D object), which occurs on both first and second presentations of possible objects, the new structural representation allows recognition of repeated presentations as individual objects (analogous to the above argument for unfamiliar faces in Henson et al., 2000). For impossible objects on the other hand, perception (of a 3D object) cannot occur on either first or second presentations, so the fusiform is not activated, and neither repetition suppression nor repetition enhancement result.

Fusiform repetition enhancement has not always been found for unfamiliar faces (Henson et

[2] This representation was assumed to be perceptual in nature (e.g, a new Face Recognition Unit, Goshen-Gottstein & Ganel, 2000), and clearly would not have the same semantic associations as those for famous faces, though it might be sufficient for an explicit recognition memory decision (which is well above chance under these conditions, Henson et al., 2002). Note that such representations were less likely to be formed for the two-tone images in the George et al. (1999) study, for which explicit recognition was likely to be poor.

al., submitted; 2002) or unfamiliar possible objects (van Turennout et al., 2000; Vuilleumier et al., 2002). This may reflect additional sensitivity of repetition effects to the task (Henson et al., 2002) or the repetition lag (Henson et al, 2000). What is found consistently is an interaction between familiarity and repetition in the midfusiform, with greater repetition suppression for familiar than unfamiliar stimuli. Repetition suppression for unfamiliar stimuli is seen in more posterior visual regions, such as lateral occipital cortex (Henson et al., 2002; van Turennout et al., 2000; Vuilleumier et al., 2002, see below). This suppression may reflect repetition of earlier visual processes common to familiar and unfamiliar stimuli.

In summary, a simple hypothesis – that repetition suppression occurs when the same process is performed on initial and repeated presentations, whereas repetition enhancement occurs when a new process occurs on repetition – can explain quite a complex pattern of fusiform repetition effects in indirect memory tasks using faces. In the case of the right midlateral fusiform, these processes are assumed to include both face perception and face recognition. This secondary assumption receives independent support from other contrasts in these studies, such as the greater response to primed faces than primed objects in the Dolan et al. (1997) study (i.e, face perception), greater responses to unprimed positive than unprimed negative images of famous faces in the George et al. (1999) study (face recognition) and greater responses to initial presentations of famous than initial presentations of unfamiliar faces in the Henson et al. (2000) study (face recognition). These processes may in fact generalise to other types of visual object (including, for example, familiar and unfamiliar symbols, Henson et al., 2000). The extent to which this hypothesis extends to other priming paradigms remains to be tested.

IV. Visual object priming: priming as a tool

If one assumes that repetition of the same process on initial and repeated stimulus presentations produces a response decrease, then this repetition suppression can be used as a tool to investigate the nature of the processes performed in different brain regions. This logic has been applied most extensively to visual object processing, by testing whether repetition suppression generalises across various changes in the visual stimulus. For example, if a region shows equivalent levels of repetition suppression for objects depicted from either the same or different viewpoint, then the processes subserved by that region can be assumed to operate over view-independent (or object-based) representations. More generally, the logic is, if region R shows reduced repetition suppression to a target that differs from the prime only on dimension D, then the processes subserved by region R are sensitive to dimension D. This is analogous to the way that behavioural priming has been used to investigate different stages in object processing (Biederman & Cooper, 1991).

Moreover, it has been claimed that such an approach is particularly useful in neuroimaging because it offers greater spatial resolution (Grill-Spector et al., 1999; Naccache & Dehaene, 2001). This argument behind this “hyper-resolution” is that a voxel sampled by fMRI or PET may contain a mixture of neurons with different selectivities (Figure 2A). Though the spatial distribution of neural firing within that voxel may distinguish two stimuli, the mean level of activity may not. However, if these neurons fire less vigorously following prior presentation of the same stimulus (i.e., habituate or adapt) the mean activity levels will differ, and therefore the region will show repetition suppression effects that are detectable with fMRI or PET.

This logic was first used by Grill-Spector et al. (1999) in a blocked fMRI paradigm. The response in the lateral occipital complex (LOC), which includes lateral occipital and posterior

fusiform regions, decreased as the frequency of object repetition within a block increased (a technique they called "fMR-adaptation"). The degree to which this adaptation was sensitive to variations in the repeated objects was used to isolate the representational level of different regions within LOC. For example, a more anterior part of LOC (in posterior fusiform gyrus and occipitotemporal sulcus) was invariant to the size and location of the object, but not to the illumination or viewpoint of the object, implicating this region in nonretinotopic but view-based (rather than fully object-based) representations.

One problem with the approach of Grill-Spector et al. (1999), in which the size of the stimulus set is varied across blocks, is that participants are likely to anticipate different frequencies of repetitions (particularly if a direct memory task like a "one-back task" is used). In such cases, any adaptation may simply reflect decreases in attention. Moreover, the relationship between multiple, short lag repetitions and the single, long-lag repetition used in typical "priming" experiments, needs to be established (immediate repetition in particular may be a special case, Bentin & Moscovitch, 1988; Nagy & Rugg, 1989). Indeed, it may be useful to distinguish neural "adaptation", which is likely under the short-lag, high-frequency repetition conditions of the Grill-Spector et al. (1999) paradigm, from neural "response suppression", which occurs after a single presentation and can be long-lasting (see Section VI).

Event-related fMRI paradigms allow repeated and nonrepeated stimuli to be randomly intermixed, such that participants cannot anticipate repetitions. Kourtzi and Kanwisher (2000), for example, compared event-related responses to pairs of trials in which either the same or different object was depicted, and varied the order of such trial-pairs unpredictably. The immediate repetition in this particular design may still represent a special case however. An event-related approach to long-lag priming was taken by Vuilleumier et al. (2002). The aim of this study was to simultaneously examine effects of viewpoint-changes and size-changes on visual object processing. Participants made object-decisions to real or "nonsense" objects (Figure 3A), reaction times for which showed priming in all cases. However, though the magnitude of the priming effect for objects was independent of size-changes, it was greater for objects repeated in the same than different view (Tarr et al., 1998).

Bilateral lateral occipital regions (e.g, -48 –75 –3) showed similar levels of repetition suppression for both real and nonsense objects (Figure 3B). This is consistent for a role of these regions in general shape extraction, prior to object recognition (Malach et al., 1995). Bilateral middle (e.g, +42 –57 –18) and left anterior (-33 –36 –27) fusiform however showed greater repetition suppression for real than nonsense objects, suggesting a role in object recognition (as in Section III).[3]

Despite the fact that early retinotopic regions showed greater responses to large than small objects, as expected, such size-changes did not interact with repetition effects in any brain region. This suggests that object repetition effects only emerge after location-invariant (nonretinotopic) representations have been accessed. View-changes on the other hand revealed an interesting lateralisation of fusiform responses. Whereas right midfusiform showed an interaction between view-changes and repetition effects, with greater repetition suppression for same than different views, the left midfusiform showed similar levels of repetition suppression for same and different views (Figure 3C). In other words, the left fusiform exhibited view-invariance, whereas the right fusiform exhibited view-specificity.

[3] Unlike Schacter et al. (1995), no repetition enhancement was found for nonsense objects in the present study (even though the nonsense objects were still possible 3D structures; see Section III). The nature of fusiform repetition effects for unfamiliar objects remains unclear.

This hemispheric lateralisation is not unprecedented. Koutstaal et al. (2001) compared repetition effects across same and different exemplars of the same object category (with the same name). They found a greater effect of exemplar change in right than left fusiform. This reflected repetition suppression for both same and different exemplars in the left fusiform, but only for same exemplars in the right fusiform. In other words, it appeared that the right fusiform treated different exemplars (e.g, two different umbrellas) as different objects, whereas the left fusiform treated them as the same object. Koutstaal et al. (2001) and Vuilleumier et al. (2002) related their fusiform laterality effects to the hemispheric specialisation hypothesis of Marsolek (1995). This hypothesis is based on behavioural priming effects using split-visual field presentation, and postulates that the right hemisphere retains specific visual-form representations, whereas the left hemisphere retains more abstract representations.

However, the Vuilleumier et al. (2002) study also included a manipulation of same versus different exemplars, and did not find the same results at Koutstaal et al. (2001). Although the left fusiform generalised over different views of an object, it did not appear to generalise over different exemplars of the same object category. Only a left inferior prefrontal region (-48 +36 +12) showed repetition suppression across different exemplars (from set A to set B in Figure 3B; see legend), probably reflecting facilitation of verbal processes related to object naming. The reason for the apparent discrepancy between the Vuilleumier et al. and Koutstaal et al. studies is unclear, but may relate to the degree of visual similarity between the different exemplars of the same category (see Vuilleumier et al., 2002, for further discussion).

In summary, the results of studies like that of Vuilleumier et al. (2002) are converging on a hierarchical model of visual object processing in which object representations become more abstracted from posterior to anterior occipital/temporal regions, and possibly more abstracted in left than right hemispheres. Early retinotopic regions do not appear to show repetition effects. Rather, lateral occipital regions appear to support the earliest stage at which repetition effects emerge, and these appear to arise from size-invariant, but not view-invariant, representations that are independent of long-term object experience (i.e, are equivalent for familiar and unfamiliar objects). More anterior fusiform regions appear to support long-term knowledge of familiar objects, which appears to be view-independent in the left fusiform and view-dependent in the right fusiform. Later stages of object naming can also show repetition effects that engage components of the language system, including left inferior frontal cortex.

V. Verbal priming: priming as a tool

The same logic of using repetition effects to map functional anatomy has also been used in imaging studies of language. Behavioural priming effects across various changes in letter-case, word-form or modality, for example, have been used for many years to argue for separate stages of orthographic, morphological, phonological and/or lexicosemantic processing. A preliminary study of word repetition effects was performed by Henson (2001). Initial and repeated presentations of words and pseudowords were randomly intermixed in an event-related fMRI design. Of particular interest was the interaction between lexicality and repetition, which was seen in a left anterior temporal region (-36 -6 -33), with repetition suppression for words, and repetition enhancement for pseudowords (cf. Section III). This region may support processing of visual word-forms (or even abstract lexical representations), though other properties unique to the words (e.g, semantics) cannot be ruled-out (see below).

Other imaging studies have examined “semantic priming”, which refers to the facilitation (or inhibition) of the processing of the meaning of a target stimulus by a preceding prime. Semantic priming tends to be short-lived, restricted to immediate prime-target presentations. At least two potential contributions to semantic priming have been proposed: automatic spreading of activation in a semantic network (Collins & Loftus, 1975) and strategic/attentional effects (Posner & Snyder, 1975).

Mummery et al. (1999) varied the proportion of semantically-related prime-target across PET scans (from 0% to 100%) in order to study semantic priming within a lexical decision task. Increasing this proportion is believed to increase the relative contribution of strategic effects (Neely, 1991). Consistent with this hypothesis, the amount of priming (per target) increased as the proportion of related prime-target pairs increased. The responses in a left anterior temporal region (-40 -4 -28), close to that in Henson (2001), decreased as the proportion increased from 0 to 75%, but increased from 75% to 100%. Though difficult to interpret unambiguously, one explanation for this pattern is a combination of an automatic semantic process producing the decrease (owing to increasing levels of repetition suppression as the incidence of repeated semantic processing within the scan increased) that is offset by a strategic effect at the highest proportion of related pairs (producing the response increase, perhaps owing to nonspecific enhancement of semantic processing in that region).

In a subsequent study, Rossell et al. (in press) used event-related fMRI to compare prime-target SOAs of 200ms versus 1000ms in a lexical decision task. Automatic processes in semantic priming are assumed to dominate at short prime-target SOAs (<250ms), whereas strategic effects are assumed to become more important at longer SOAs (Neely, 1991). The only region showing repetition suppression was in left anterior temporal cortex (-40 +14 -24), slightly anterior to that observed by Mummery et al. (1999). This supports a role for this region in semantic processing. However, the amount of repetition suppression did not interact with SOA, leaving its precise role unclear.

The left anterior temporal cortex (-42 0 -30) also showed repetition suppression for blocks of sentences with the same versus different syntactic forms in a study by Nopponey and Price (submitted). A behavioural experiment confirmed priming of such sentences in the form of shorter reading times for same versus different syntactic forms. This “syntactic priming” could not reflect word-specific semantic priming, since the sentences contained different content words, but could reflect facilitation of sentence-level semantic integration (e.g., the assignment of thematic roles to sentence arguments). The above priming studies thus represent important inroads into the functional anatomy of semantic processing, and suggest future studies that may further refine the nature of the semantic processing (e.g, by factorially varying same versus different content words and same versus different syntactic frames).

In summary, by assuming that repetition suppression is as a signature of repeated processing, the investigation of various stimulus manipulations on the amount of repetition suppression offers a potentially powerful means of mapping different stages in stimulus-processing. An alternative approach is to keep the stimulus constant while varying the relationship between the tasks performed on prime and target (i.e, varying the manner in which the prime and target are processed; see Henson, submitted). In both cases however, before a brain region evidencing repetition suppression can be associated with a particular process, precautions must be taken to rule out other psychological processes, such as explicit memory or attention, that may also covary with the stimulus/task manipulations in that region (see Section VIII).

VI. Neural mechanisms of repetition suppression

A potential neural analogue of the repetition suppression observed with fMRI and PET is "response suppression" (Desimone, 1996) or "decremental responses" (Brown & Xiang, 1998). These terms refer to a decrease in the firing rate of neurons, typically recorded in inferior temporal regions of the nonhuman primate, following repetition of a stimulus. The decreased firing rate is not nonspecific habituation, because it occurs after a single exposure to a stimulus, and does not affect the firing rate to other stimuli for which the neuron is responsive.[4] Moreover, it can last hours/days and numerous intervening stimuli, though the longevity of the effect typically decreases from anterior (e.g., 24 hours in perirhinal cortex, 10mins in area TE) to posterior regions (sometimes not surviving a single intervening stimulus in temporoccipital regions, Brown & Xiang, 1998).

Wiggs and Martin (1998) extended this phenomenon to human imaging findings on priming. They proposed that repeated processing of a stimulus produces a "sharpening" of its cortical representation, whereby neurons coding features unnecessary for processing that stimulus respond less (i.e, exhibit response suppression). This results in a decrease in the mean firing rate of a population of neurons, hence a decrease in the haemodynamic response from that region of cortex (Figure 2B). This "sparser" representation then allows (somehow) faster/more accurate behavioural responses.

Though offering an attractive link between these different levels of neuroscience, there are potential complications to this simple mapping. For example, the association of neuronal response suppression with priming is yet to established in nonhuman primates, since the same phenomenon (when observed in perirhinal cortex) has been interpreted in terms of explicit, recognition memory (Brown & Xiang, 1998; see Henson, this volume). One possibility is that the same neural signal of decreased firing rates is used for different purposes in different brain regions. Secondly, a mechanistic account is needed to explain how sparser representations allow faster/more accurate processing (i.e, priming). Thirdly, the limited duration of neural response suppression in posterior occipitotemporal regions (Baylis & Rolls, 1987) is unlikely to account for the haemodynamic repetition suppression observed across days in those regions in humans (van Turennout et al., 2000). Fourthly, such a theory would not appear able to explain the greater fusiform repetition suppression effects for familiar than unfamiliar stimuli discussed in Section III, since the opposite interaction would be predicted by the Wiggs and Martin (1998) theory, namely greater repetition suppression for unfamiliar than familiar stimuli (given that the latter are already likely to have sparse representations, Li et al., 1993). See Henson and Rugg (2002) for further discussion of these issues.

Two further questions concern the relationship between neural firing rates and haemodynamic responses (aside from the physiological relationship between action potentials, local field potentials and BOLD, Logothetis et al., 2001). Even with event-related fMRI, it must be remembered that the haemodynamic response effectively integrates several seconds of neural/synaptic activity. This means that a decrease in the magnitude of the haemodynamic response may not reflect decreased neural firing rates per se, but a shortened duration of neural/synaptic activity. One way to try to distinguish these possibilities is to test for differences in the peak latency, as well as magnitude, of the event-related BOLD response. Henson and

[4] This stimulus-specific suppression thus represents a slightly different conception to the neuron-specific habituation assumed by (Grill-Spector et al., 1999) and discussed in Section IV and Figure 3A.

Rugg (2001) found that repetition of famous faces not only decreased the peak magnitude of the BOLD impulse response in a right fusiform region, but also decreased its peak latency (though not onset latency). The most parsimonious account of this combined change in BOLD magnitude and peak latency is that repetition reduced the duration of underlying neural/synaptic activity. At least one reason for a reduced duration of neural activity, in an alternative mechanism of repetition suppression, is a decreased "settling" time in an attractor neural network, following short-term weight-changes associated with processing of the prime. Such networks have been applied successfully to priming data (e.g., Plaut & Shallice, 1993)

A final question concerns the onset latency of repetition effects. Neural response suppression can be very rapid, with the shortest differential latency in perirhinal neurons equalling their visual response latency (70-80ms), and estimates of the mean population latency being as short as 150ms (Ringo, 1996). These estimates have been used to argue that response suppression (even in anterior temporal regions) is a local effect, too rapid for re-entrant (or "top-down") influences (Brown & Xiang, 1998). These latencies are shorter than the latencies of stimulus repetition effects measured with ERPs in humans, which typically onset 250-300ms (Rugg & Doyle, 1994).[5] Human intracranial ERP recordings in inferior temporal regions for example show early face-specific potentials, onsetting 150-200ms poststimulus, but no evidence that these potentials are sensitive to repetition of faces; such effects only emerge 250-300ms poststimulus (Puce et al., 1999).

These ERP data therefore raise the possibility that haemodynamic repetition suppression in humans involve later (e.g, re-entrant) effects.[6] Indeed, in an exciting study that used fMRI data to constrain the source of MEG priming-related effects in a semantic decision task to words (Dale et al., 2000), an initial wave of activity had spread to temporal, parietal and even frontal regions by 185ms. The earliest repetition effect however emerged in a left anterior inferior temporal region at 250ms, and was strongest at 385ms. These data reinforce the possibility that priming effects do not necessarily arise in a "first-pass" through the neural circuitry, and that effects in posterior regions include "top-down" influences from more anterior regions.

One possibility is that repetition effects in a region reflect changes in the prediction error fed-back from "higher" levels in a processing pathway (Friston, in press). According to this model, stimulus processing modifies the strengths of recurrent synaptic connections between different levels of a neural hierarchy, which in turn affect the dynamics of each level in settling on an interpretation (e.g., recognition) of a stimulus. In the case of repetition suppression, an increase in the synaptic efficacy of feedforward and feedback connections between two layers, following initial presentation of a stimulus, decreases the error in the lower-level between its bottom-up (stimulus-related) and top-down (prediction-related) inputs when that stimulus is repeated. This reduced error may result in more rapid stimulus recognition, and a reduced haemodynamic response in the lower region. The important perspective offered by this model is that priming reflects interactions between different brain regions. The specific regions will then depend on the set of component processes engaged by the stimulus and task.

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[5] Earlier repetition-effects of 100-200ms have been reported in some ERP studies, but usually for immediate repetition (Nagy & Rugg, 1989, though see George et al., 1997, and Tsivilis et al., 2001, for exceptions).

[6] As with any imaging study, it must be remembered that, just because activations occur in brain regions associated with "early" stages of visual processing, this does not mean that differences in the underlying neural activity occur early in time.

VII. Pharmacological challenges

The cholinergic system influences neural plasticity, and has been shown to modulate explicit memory (e.g, Curran et al., 1998; see also Coull & Thiel, this volume). Its role in implicit memory is more controversial, since the administration of a cholinergic blocker (such as the drug scopolamine, a acetycholine antagonist) has not been found to affect measures of priming in some studies (Schifano & Curran, 1994; though see below). Furthermore, scopolamine does not appear to affect the neural phenomenon of response suppression (Section VI; Miller & Desimone, 1993). By contrast, modulations of the GABAergic system (by the drug lorezapam for example, a GABA agonist) do affect priming (Vidailhet et al., 1999).

Thiel et al. (2001) examined the effects of both scopolamine and lorezapam on repetition suppression in an event-related fMRI study of word-stem completion. Both drugs were found to reduce behavioural measures of priming, consistent with previous studies using lorezapam, but contrary to previous studies using scopolamine. This suggests that cholinergic blockage can impair some forms of priming (one reason why such an effect was not seen in previous studies may be that they used smaller doses of scopolamine). Both drugs also reduced the amount of repetition suppression in left extrastriate occipital cortex (-36 -75 -6) and left inferior (-45 +39 -9) and posterior (-39 -3 54) frontal cortex (Figure 4A), regions associated with word-stem priming in the placebo group and in previous studies (e.g, Buckner et al., 2000).[7]

The reason for the reduced repetition suppression under the drugs was a reduced response to unprimed stems, relative to the placebo group (except for the extrastriate region in the scopolamine group, Figure 4A). This suggests that the drugs impaired initial processing of the stimuli, perhaps impairing the registration of stimulus information, and so not affecting the response when the stimuli were repeated. The failure to find an effect of scopolamine on neural measures of response suppression (Miller & Desimone, 1993) may reflect differences between the haemodynamic and neural indices (see Section VI), or differences in the experimental paradigms (e.g, the task, or the repetition lag).

Thiel et al. (2002) examined effects of the same drugs within a face-priming paradigm. Participants made speeded familiarity-decisions to familiar and unfamiliar faces, half of which had been presented in a previous study phase. In this case, reduced priming, in the form of decreased RTs for familiar but not unfamiliar faces, was found with scopolamine, but not with lorezapam. A right fusiform region (+30 –45 –30) showed similar familiarity-by-repetition interactions in the placebo and lorezapam groups, with greater repetition suppression for familiar than unfamiliar faces (see Section II), but this interaction was not significant in the scopolamine group (Figure 4B, though no interactions between the scopolamine and placebo groups reached significance either). These data support those of Thiel et al. (2001) in suggesting that cholinergic blockage can attenuate priming. They also suggest that the effect of GABAergic modulation on priming (at least with lorezapam) may depend on the specific priming task (e.g, identification versus production tasks, Gabrieli et al., 1999).

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[7] It is possible that scopolamine affects arousal and/or explicit memory in this paradigm. However, the priming effects did not correlate with various measures of sedation, or with global haemodynamic estimates. Moreover, a concurrent manipulation of the degree of semantic processing at study (which improves explicit memory, see Henson, this volume) did not interact with the amount of priming. This argues against explicit memory contamination of the behavioural measures (though it remains possible that differences in explicit memory contaminated the haemodynamic measures).

Thiel et al. (2002) performed a further behavioural study on an independent group of participants, in which scopolamine was administered after the study phase. In this case, priming did not differ significantly from a placebo group. This supports the assumption that cholinergic blockade affects the acquisition rather than expression of priming.

A study by Bentley et al. (submitted) examined the effects of physostigmine, a cholinesterase inhibitor (i.e, having effects broadly complementary to those of scopolamine). This study also manipulated the factors of attention and emotion in a face/house matching paradigm. Two pairs of stimuli were presented simultaneously, one pair above and below a central fixation point (vertical locations), and the other pair left or right of fixation (horizontal locations). In each trial, one stimulus pair consisted of the same or different (unfamiliar) faces, and the other consisted of the same or different (unfamiliar) houses. Prior to a block of trials, participants were cued to respond "same" or "different" to the two stimuli appearing in either the vertical locations, or in the horizontal locations. This way, covert spatial attention could be directed towards either faces or houses.

The critical stimuli were the face pairs, which repeated across 2-5 intervening trials (the repetition factor). Each face pair also consisted of either neutral or fearful faces (the emotion factor) and could occur in either attended or unattended locations (the attention factor). Note that either both presentations of a face-pair were attended, or both presentations were unattended. For the placebo group, reaction times showed priming for neutral but not fearful faces when attended (for unattended faces, reaction times pertain to match decisions for the houses, for which the notion of priming is unclear). The lack of priming for fearful faces may reflect automatic orienting or attentional capture that counteracts any facilitation due to prior processing. This interaction between repetition and emotion for attended faces was absent in the physostigmine group however.

A right occipital region (+40 –78 –18) in the placebo group showed repetition suppression for both attended and unattended face-pairs, regardless of face emotion (Figure 4C). Interestingly, a parahippocampal region (-22 –32 –10) showed repetition enhancement for unattended faces (i.e, when houses were task-relevant), possibly reflecting reduced interference from "distracting" faces. Assuming that the paradigm was successful in abolishing attention to task-irrelevant locations (as suggested by Vuilleumier et al., 2001), the occipital findings suggest that some brain regions can show automatic repetition suppression in the absence of top-down modulation (cf. Section VI).[8] Under physostigmine however, repetition suppression in these regions was only found for attended faces. Indeed, a left occipital region (-34 –68 –22; not shown) showed greater repetition suppression under physostigmine than under placebo, but only for attended faces. This is consistent with the suggestion that cholinergic enhancement selectively facilitates processing of attended stimuli (Sarter et al., 2001).

An interaction between repetition and emotion for attended (but not unattended) faces was found in right lateral orbitofrontal cortex (+38 +38 –14) for the placebo group, with greater suppression for neutral than fearful faces (Figure 4C), paralleling the behavioural data. This interaction appeared to reverse under physostigmine however, with greater relative repetition suppression for emotional faces. This is consistent with cholinergic enhancement of the processing of emotional stimuli (Holland & Gallagher, 1999).

[8] Note that these lateral occipital repetition suppression effects for unfamiliar faces resemble those found by Henson et al. (2002), and are posterior to the fusiform regions that did appear sensitive to top-down modulation in that study.

In summary, pharmacological manipulations, such as those that affect the cholinergic system, can be shown to interact with behavioural measures of priming and their putative underlying haemodynamic correlates. The interactions are complex, depending on the specific priming task, levels of attention, valence of the stimuli, and probably factors like dose levels and time of administration. Nonetheless, pharmacological manipulations may offer one way to dissociate implicit and explicit contributions to repetition effects, and also provide an important means to get at the mechanisms underlying neural (and haemodynamic) repetition effects, particularly in conjunction with artificial neural network models (e.g., Sohal & Hasselmo, 2000).

VIII. Conclusion

This chapter has described studies selected from the Wellcome Department of Imaging Neuroscience that combine functional imaging with the behavioural phenomenon of repetition priming. Several themes have been discussed: 1) A simple hypothesis that distinguishes repetition suppression and repetition enhancement, using face priming as an example, 2) the use of repetition suppression as a tool for functional mapping, illustrated with examples from visual object and verbal semantic priming, 3) possible neural mechanisms underlying haemodynamic repetition effects, and 4) the value of pharmacological manipulations.

Several caveats remain to be addressed. Foremost, no imaging study to date has ruled out explicit memory contamination of repetition effects (except for studies of masked priming, e.g. Dehaene et al., 2001), which may represent a special case, Henson, submitted). Some simple precautions to minimise explicit memory include the use of speeded responses, switching the task performed on prime and target (also ruling out facilitation of low-level response contingencies) and experimental manipulations known to reduce explicit memory encoding (e.g., divided attention at study). However, even though explicit memory may be shown not contribute to a concurrent behavioural measure of priming (e.g., if speeded decisions to a target are too fast for recollection to play a role), because PET and fMRI average activity over seconds, the resulting haemodynamic changes may include effects of processes operating subsequent to the behavioural response, such as incidental recollection of the prime. A better solution is to use paradigms in which explicit memory for repetition is also measured (e.g, Schott et al., 2002), or even to use direct memory paradigms (e.g, focussing on old items that are “missed” in a recognition memory task; see Henson, this volume). The scanning of amnesic patients (or normal participants under the influence of certain drugs, Section VII) may be another way to minimise explicit memory, provided priming is still intact.

A second caveat is the question of cause and effect. Reduced responses to repeated stimuli in regions of interest may be an effect, rather than the cause, of behavioural priming effects. Repetition suppression in the fusiform, for example, may reflect diminished attention to the stimulus, or shortened gaze duration, as a consequence of priming-related facilitation in other brain regions. Questions like these are difficult to answer with imaging techniques alone, and would benefit from concurrent demonstrations of reduced priming in patients with damage to the region of interest (e.g, Keane et al., 1995), or following transcranial magnetic stimulation (TMS) of that region. Another approach is to use haemodynamic data to help localise MEG/EEG effects, and argue for cause or effect on the basis of temporal precedence in the timecourse of repetition effects.

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Figure Legends

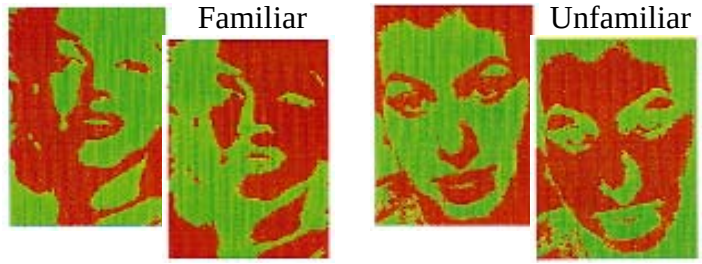
Figure 1.
Schematic of the hypothetical processes of perception and recognition occurring for unprimed and primed face presentations across the studies of A) Dolan et al. (1997), B) George et al. (1999) and C) Henson et al. (2000). Examples of the stimuli used in each study shown on the right. A combination of these two processes, together with a simple hypothesis about their haemodynamic correlates (see text), can explain the complex pattern of repetition effects across the three studies.

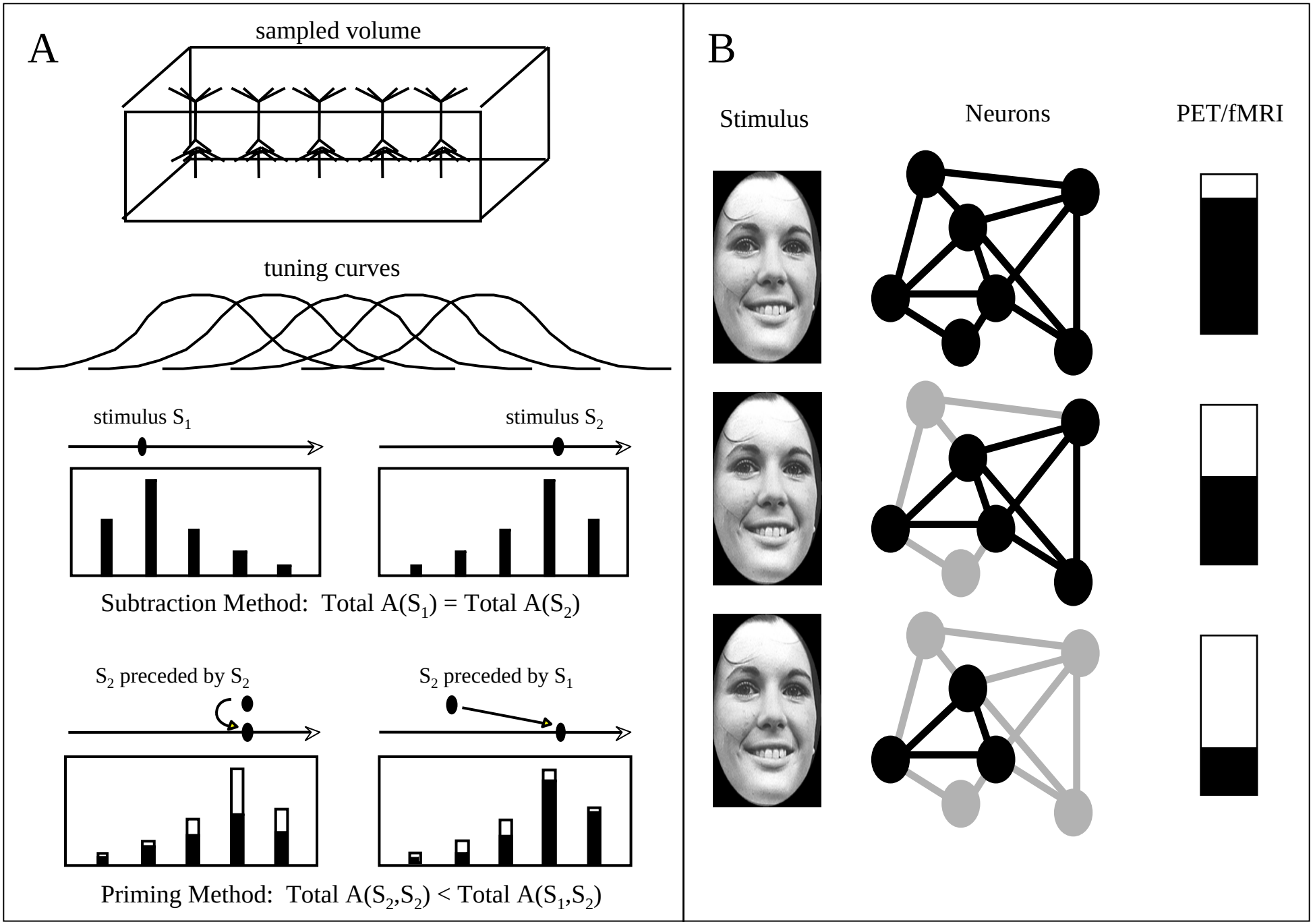
Figure 2.
A) Schematic of hyper-resolution argument of Grill-Spector et al. (1999) and Naccache & Dehaene (2001). Automatic, neuron-specific adaptation may reveal haemodynamic differences in an image voxel that encompasses many neurons with different tuning curves, even when a conventional subtraction of two different stimuli may not. Adapted with permission from Stan Dehaene. B) Sharpening theory of Wiggs and Martin (1998) in which repetition of a stimulus (left column) produces stimulus-specific response suppression in some neurons (greyed out in middle column), which "drop out" of the stimulus representation, and a decrease in the haemodynamic response (repetition suppression; right column).

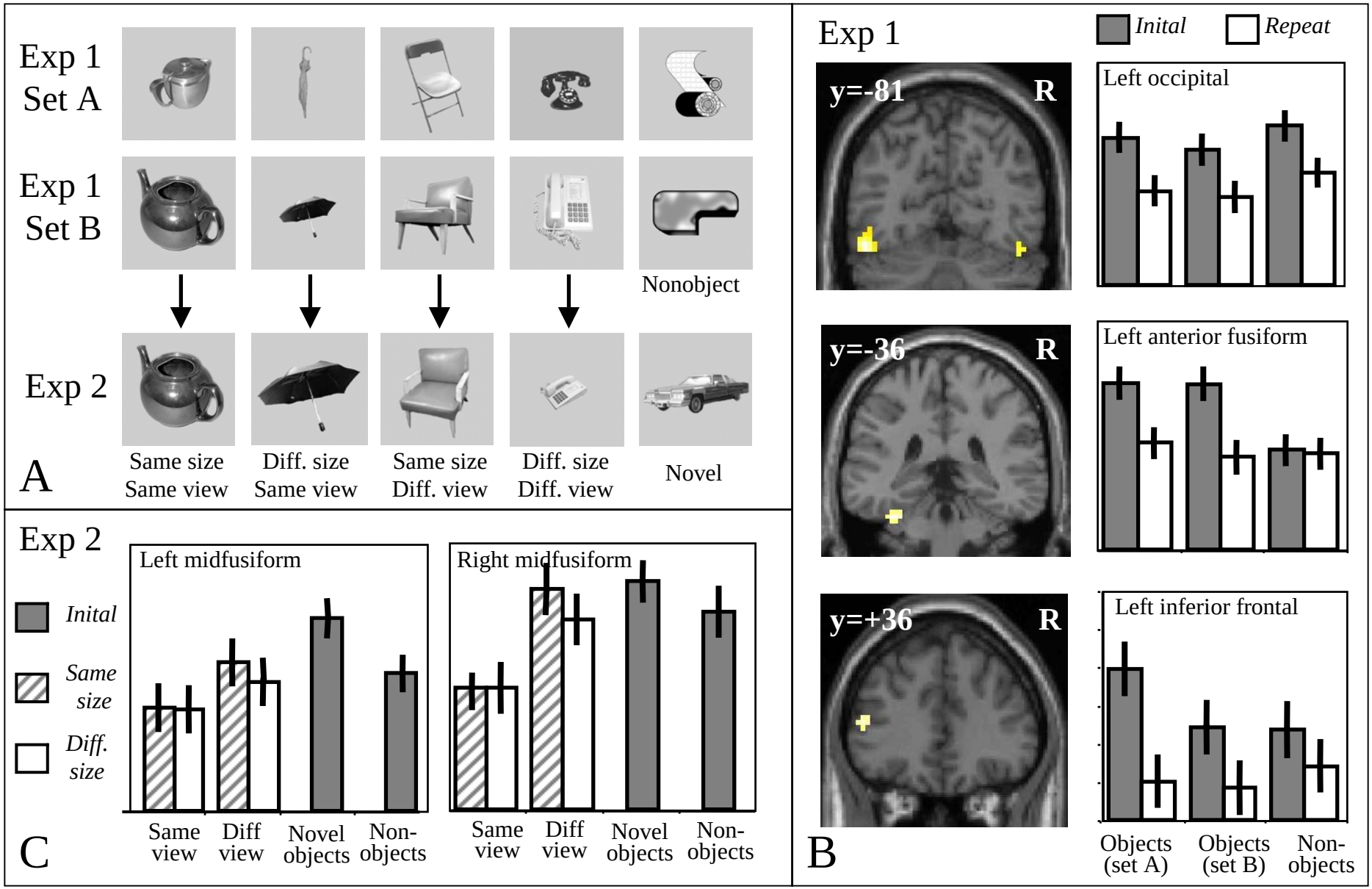
Figure 3.
A) Stimuli and conditions in Vuilleumier et al. (2002). Sets A and B contained different exemplars of a category with the same basic-level name. In Experiment 1, Set A was presented before Set B, such that the first presentation of a Set B object was preceded by a different exemplar with the same name. In Experiment 2, objects from one or other set in Experiment 1 were repeated in either the same or different size, and from the same or different viewpoint, together with novel objects not seen in Experiment 1. Nonobjects were present in both experiments, and participants performed an object-nonobject decision. B) Canonical response parameter estimates in Experiment 1 from left occipital cortex (top), showing repetition suppression for both objects and nonobjects, from left anterior fusiform (middle), showing repetition suppression for objects only, and from left inferior frontal cortex (bottom), in which first presentations of Set B objects showed repetition suppression relative to first presentations of Set A objects. C) Canonical response parameter estimates in Experiment 2 from left and right midfusiform regions: left midfusiform showed repetition suppression across different sizes and different views, whereas right midfusiform showed repetition suppression only across same views.

Figure 4.
A) Left extrastriate, inferior frontal and dorsal frontal regions from Thiel et al. (2001), together with canonical response parameter estimates to unprimed and primed word-stems in Placebo, Lorazepam and Scopolamine groups. B) Right midfusiform from Thiel et al. (2002), together with canonical response parameter estimates to first and second presentations of familiar (F1 and F2) and unfamiliar (U1 and U2) faces in the Placebo, Lorazepam and Scopolamine groups. C) Right inferior occipital and orbitofrontal regions from Bentley et al. (submitted), together with canonical response parameter estimates in the 8 experimental conditions (A=attended, U=unattended; N=neutral, E=emotional; 1=first and 2=second face-pair presentation) for the Placebo and Physostigmine groups.

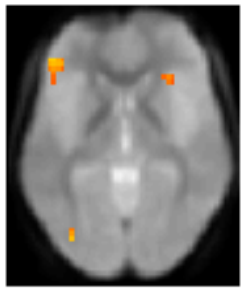
	Unprimed	Primed		Repetition effect
A. Dolan et al (1997)				
Perception	✗	✓	=>	enhancement
Recognition	✗	✗		
B. George et al (1999)				
Perception	✓	✓	=>	suppression
Recognition	✗	✗		
Perception	✓	✓		
Recognition	✗	✓	=>	enhancement
C. Henson et al (2000)				
Perception	✓	✓		
Recognition	✗	✓	=>	enhancement
Perception	✓	✓		
Recognition	✓	✓	=>	suppression

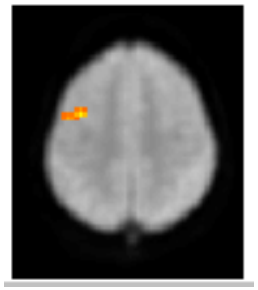


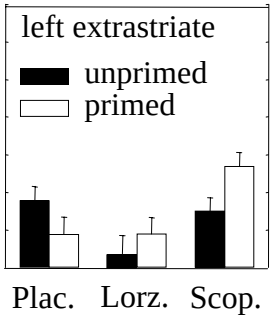

A
sampled volume
tuning curves
stimulus S_1
stimulus S_2
Subtraction Method: Total $A(S_1)$ = Total $A(S_2)$
S_2 preceded by S_2
S_2 preceded by S_1
Priming Method: Total $A(S_2,S_2)$ < Total $A(S_1,S_2)$
B
Stimulus
Neurons
PET/fMRI

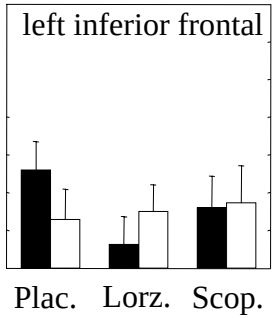

Exp 1
Set A
Exp 1
Set B
Nonobject
Exp 2
A
Same size
Same view
Diff. size
Same view
Same size
Diff. view
Diff. size
Diff. view
Novel
Exp 2
Inital
Same size
Diff. size
Left midfusiform
Right midfusiform
Same view
Diff view
Novel objects
Non-objects
C
Exp 1
Inital
Repeat
y=-81
R
Left occipital
y=-36
R
Left anterior fusiform
y=+36
R
Left inferior frontal
Objects (set A)
Objects (set B)
Non-objects
B

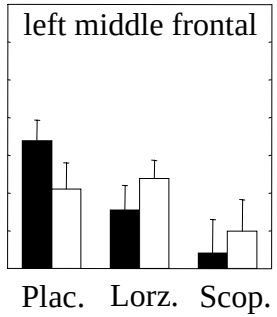
A



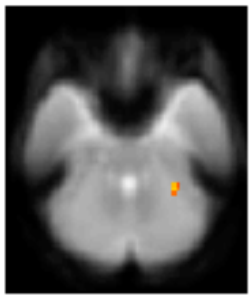


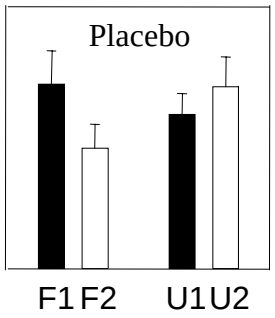

left extrastriate
unprimed
primed
Plac. Lorz. Scop.

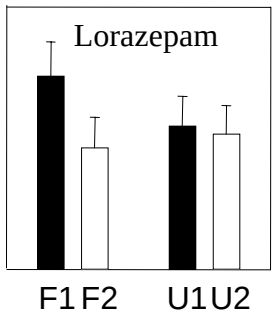

left inferior frontal
Plac. Lorz. Scop.

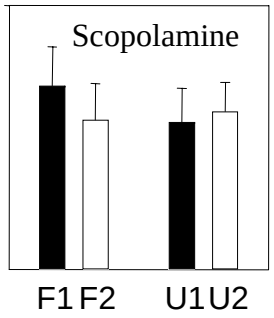

left middle frontal
Plac. Lorz. Scop.

B

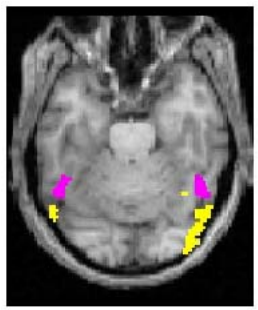


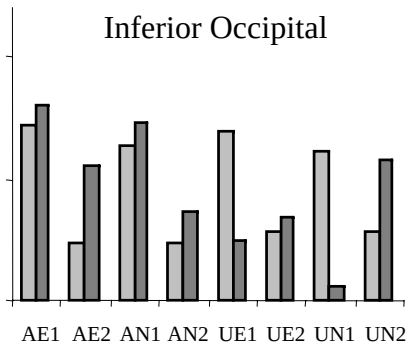

Placebo
F1 F2 U1 U2

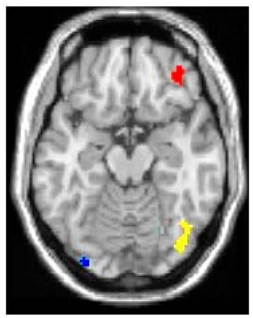

Lorazepam
F1 F2 U1 U2

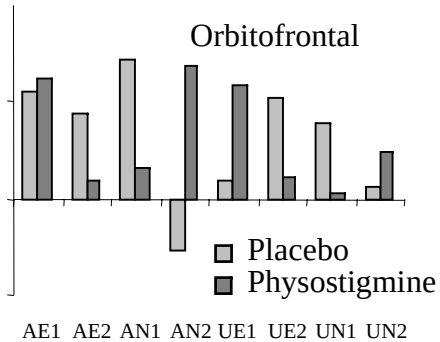

Scopolamine
F1 F2 U1 U2

C




Inferior Occipital
AE1 AE2 AN1 AN2 UE1 UE2 UN1 UN2




Orbitofrontal
Placebo
Physostigmine
AE1 AE2 AN1 AN2 UE1 UE2 UN1 UN2