Further dissociating the processes involved in recognition memory: an fMRI study

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Abstract

Based on an ERP study by Rugg et al. (1998), we attempted to isolate the hemodynamic correlates of recollection, familiarity and implicit memory within a single verbal recognition memory task using event-related fMRI. Words were randomly cued for either deep or shallow processing, and then intermixed with new words for yes/no recognition. The number of studied words was such that, while most were recognized ("hits"), an appreciable number of shallow-studied words were not ("misses"). Comparison of deep hits versus shallow hits at test revealed activations in regions including left inferior parietal gyrus. Comparison of shallow hits versus shallow misses revealed activations in regions including bilateral intraparietal sulci, left posterior middle frontal gyrus and left frontopolar cortex. Comparison of hits versus correct rejections revealed a relative deactivation in an anterior left medial temporal region (most likely perirhinal cortex). Comparison of shallow misses versus correct rejections did not reveal response decreases in any regions expected on the basis of previous imaging studies of priming. Given these and previous data, we associate the left inferior parietal activation with recollection, the left anterior medial temporal deactivation with familiarity, and the intraparietal and prefrontal responses with target detection. The absence of differences between shallow misses and correct rejections means that the hemodynamic correlates of implicit memory remain unclear.

At least three different expressions of memory have been associated with repetition of a stimulus: recollection, familiarity and priming. Recollection and familiarity are examples of conscious or explicit memory, whereas priming is an example of unconscious or implicit memory (Schacter & Tulving, 1994). Recollection refers to retrieval of contextual information associated with a prior encounter with a stimulus; familiarity refers to a feeling that the stimulus has been encountered previously in the absence of retrieval of associated contextual information (Mandler, 1980; Yonelinas, 2002). Priming refers to a change in behavioral response to the stimulus in the absence of explicit memory for its prior occurrence (Schacter, 1987; Roediger & McDermott, 1993).

The extent to which these three types of memory depend on functionally distinct processes is a matter of debate. For example, it remains contentious whether one needs to distinguish recollection and familiarity in order to explain behavioral dissociations within recognition memory tasks (Yonelinas, 2002 vs. Heathcote, 2003), or neuropsychological dissociations between recall and recognition performance (Yonelinas et al., 2002 vs. Wixted & Squire, 2004). It also remains uncertain whether familiarity and priming are independent forms of memory, or consequences of the same underlying cause. According to some views for example, familiarity and priming both arise from increased fluency of conceptual/perceptual processing, differing only in whether that fluency is attributed to a past encounter (Jacoby & Dallas, 1981; Whittlesea & Williams, 2000). Neuropsychological evidence for this dissociation between explicit memory and priming is unresolved (Wagner et al., 1998; Stark & Squire, 2000; vs. Ostergaard, 1999; Kinder & Shanks, 2003). In light of the ambiguous nature of behavioral and neuropsychological findings, converging evidence for or against these distinctions is of particular importance. One line of evidence takes the form of non-invasive measures of brain activity, which can be employed to examine whether the three types of memory are associated with qualitatively different patterns of activity in the brain, using electrophysiological measures such as event-related potentials (ERPs) or, as here, hemodynamic measures

such as event-related fMRI.

The present experiment followed the same rationale as that employed by Rugg et al. (1998). At study, words were pre-cued for either a semantic decision ("Deep" task) or orthographic decision ("Shallow" task) on a trial-by-trial basis. At test, participants were asked to distinguish the studied words ("Old" items) from other words that were not studied ("New" items). This rationale, which can be criticized and is certainly subject to important caveats (see Discussion), is as follows: Given evidence that semantic encoding increases the likelihood of recollection at test more than it does familiarity-driven recognition (Yonelinas, 2002), recollection was operationalized by the comparison of "Deep Hits" (old items that were studied under the semantic task and correctly recognized) versus "Shallow Hits" (old items that were studied under the orthographic task and correctly recognized). Because recognition following shallow encoding tasks such as that employed here is largely familiarity-driven (Yonelinas, 2002), familiarity was operationalized by the comparison of "Shallow Hits" versus "Shallow Misses" (old items that were studied under the orthographic task but not correctly recognized). Finally, making the assumption that studied items that are not recognized at test are not associated with explicit memory, implicit memory was operationalized by the comparison of "Shallow Misses" with "Correct Rejections" (new items that were correctly identified as unstudied).

It is important to note that these particular operationalizations of recollection, familiarity and implicit memory can be re-interpreted according to different models of memory (specifically with regard to the effects of study task and decision processes at test), as described in the Discussion. Nonetheless, the presence of some form of qualitative differences is supported from the findings of Rugg et al. (1998), who reported a dissociable ERP effect associated with each of the above comparisons. The aim of the present study was to see whether we could find analogous hemodynamic dissociations. As well as looking for dissociations at test, we also examined hemodynamic differences at study that correlated with subsequent memory at test (eg,

Paller & Wagner, 2002). The present study is by no means the first to attempt to dissociate different forms of memory (for reviews, see e.g, Buckner & Wheeler, 2001; Mayes & Montaldi, 2001; Rugg et al., 2002), and findings from previous studies provide important information about the likely regions involved in each case. Though some of these studies have reported dissociations between, for example, various operationalizations of recollection and familiarity (e.g, Henson et al., 1999b; Eldridge et al., 2000; McDermott et al., 2000; Cansino et al., 2002; Dobbins et al., 2003; Wheeler & Buckner, 2004; Yonelinas et al., submitted), or between explicit memory and priming (e.g, Schott et al., submitted), we are not aware of an imaging study that has managed to dissociate all three types of memory within the same experimental design.

Results

Behavioral Results

The behavioral data are shown in Table 1. Following predictions based on Rugg et al. (1998), the data were tested with a series of one-tailed paired t-tests. Deep Hits were more common than Shallow Hits, $t(20)=10.4$, $p<.001$, consistent with a levels of processing effect (Craik & Lockhart, 1972). Shallow Hits were more common than False Alarms, $t(20)=15.7$, $p<.001$, confirming that they were more than guesses (pH-pFA = .48).

At Study, RTs for subsequent Shallow Hits and Shallow Misses were slower than for subsequent Deep Hits, $t(20)$'s>8.62, p's$<.001$. In other words, as expected, it took longer to decide whether the first and last letters of a word were in alphabetical order than whether the word referred to an animate entity. Shallow Hit RTs did not differ significantly from Shallow Miss RTs, $t(20)=-0.82$, $p=.21$. Both of the above RT findings suggest that subsequent memory does not correlate simply with the time spent responding to stimuli at study.

At Test, Deep Hits were faster than Shallow Hits, $t(20)=5.06$, $p<.001$, and Correct Rejections, $t(20)=5.20$, $p<.001$. Shallow Hit RTs did not differ from Correct Rejection RTs, $t(20)=0.18$, $p=.43$. Shallow Misses were slower than all three other

conditions, $t(20)$'s>6.15, p's$<.001$.

efMRI Results

We describe results from the Study phase first, followed by results from the Test phase.

Comparisons at Study

At Study, there were two contrasts of interest: subsequent Deep Hits versus subsequent Shallow Hits, and subsequent Shallow Hits versus subsequent Shallow Misses. The former indexes depth of processing (semantic vs. orthographic), while holding subsequent recognition success constant (though the nature of the retrieved information underlying that success may differ, see Discussion); the latter indexes subsequent recognition success, while holding type of processing constant.

Depth of processing effects

The regions showing greater responses to subsequent Deep Hits than subsequent Shallow Hits are highly consistent with previous comparisons of semantic versus non-semantic processing of words (e.g, Wagner et al., 1998; Otten et al., 2001), most notably left anterior inferior frontal gyrus, anterior and superior medial frontal gyrus and bilateral temporal poles (Table 2; Figure 1A). Also notable were greater responses in regions of the medial temporal lobe (MTL), namely a left anterior MTL region that extended posteriorly into what is most likely the hippocampus, and bilateral regions within parahippocampal cortex. Both of these MTL regions showed greater responses for Deep Hits than either Shallow Hits or Shallow Misses (Figure 1A).

Several regions showed greater responses to subsequent Shallow Hits than subsequent Deep Hits, most notably extensive parts of bilateral intraparietal and bilateral dorsolateral prefrontal cortex (data not shown; available on request).

Subsequent Memory effects (under shallow task)

The regions showing greater responses to subsequent Shallow Hits than subsequent Shallow Misses are shown in Table 3/Figure 1B. Most notable on the basis of previous studies of subsequent memory effects under "shallow encoding"

tasks (Otten & Rugg, 2001a; Baker et al., 2001; Fletcher et al., 2003) were regions stretching along the left and right inferior frontal sulci/middle frontal gyri, and bilateral inferior parietal and fusiform cortices. The anterior aspect of the left frontal cluster and the bilateral fusiform regions showed greater responses for both Deep Hits and Shallow Hits relative to Shallow Misses (Figure 1B), with little evidence of a difference between Deep and Shallow Hits (if anything, a trend for less response for Deep than Shallow Hits in the fusiform regions).

There were parts of the extensive left frontal cluster that overlapped with the left mid inferior gyrus region (BA 45) that showed a depth of processing effect, though the cluster showing a subsequent memory effect was generally more superior, within and above the inferior frontal sulcus (cf. Figure 1A and 1B). Part of the left inferior parietal cluster, particularly around the angular gyrus (BA 39), also overlapped with the angular gyrus region that showed depth of processing effects (Figure 1C).

No regions showed reliably greater responses to subsequent Shallow Misses than subsequent Shallow Hits.

Comparisons at Test

We first tested the basic "old-new effect" (Hits versus Correct Rejections, collapsing across Deep and Shallow Hits), for comparison with previous studies. We then attempted to isolate recollection, familiarity and implicit memory using the three operationalizations given in the Introduction.

Basic Old-New effects

The regions showing greater responses to Hits than Correct Rejections were highly consistent with previous studies (Rugg & Henson, 2002), most notably extensive parts of bilateral inferior and superior parietal cortices, intraparietal sulci, bilateral precuneus, posterior cingulate and left frontopolar cortex (Table 4).

Only one region showed a greater response to Correct Rejections than Hits, in left anterior MTL, most likely perirhinal cortex (Figure 2). This finding is of interest because it replicates the pattern found in (left and/or right) anterior MTL in a previous

meta-analysis across four studies (Henson et al., 2003). Post hoc tests indicated that this relative "deactivation" was found for both Shallow (t(20)=4.46, p<.001) and Deep (t(20)=2.29, p<.05) Hits relative to Correct Rejections. The response for Shallow Misses fell approximately midway between that for Shallow Hits and that for Correct Rejections, but did not differ significantly from either (t(20)<1.39, p>.09). Interestingly, this region was close to the anterior MTL region that showed a depth of processing effect at study, which also extended more posteriorly into hippocampus. Indeed, the present perirhinal region showed evidence (t(20)=3.12, p<.005) of a depth of processing effect, but not of a subsequent memory effect, at study (Figure 2).

Deep versus Shallow Hits

Regions showing differential responses between Deep and Shallow Hits, the present operationalization of recollection, are shown in Table 5. Most notable on the basis of previous studies (e.g, Henson et al., 1999b; Wheeler & Buckner, 2004) was the greater relative response to Deep Hits in inferior parietal cortex, particularly on the left around angular gyrus. This cluster overlapped with that showing a depth of processing effect at study (and close to that showing a subsequent memory effect at study, Figure 1C). The region was more responsive to Deep Hits than the remaining three trial-types, which did not differ reliably (Figure 3A). A similar pattern was seen in the right supramarginal gyrus region. The remaining two regions in anterior and posterior middle temporal gyrus were not predicted, and showed an unusual pattern of a smaller response to Shallow Hits than either Deep Hits or Shallow Misses (Figure 3A).

Two regions were relatively more responsive for Shallow Hits than Deep Hits: in anterior cingulate and occipital cortex. These responses may have reflected the greater relative difficulty (and longer RTs) in recognizing shallowly- than deeply-studied items.

Shallow Hits versus Shallow Misses

Regions showing greater responses for Shallow Hits than Shallow Misses, the present operationalization of familiarity, are shown in Table 6. All regions were of

interest on the basis of previous studies (Rugg & Henson, 2002), namely bilateral intraparietal sulcus (extending into superior parietal gyrus on the left), bilateral precuneus, left middle frontal gyrus and left frontopolar cortex (superior frontal gyrus). These regions showed response increases for Deep and Shallow Hits relative to Shallow Misses and Correct Rejections (shown for the left superior parietal and left frontopolar regions in Figure 3B). The middle frontal gyrus region showed a similar pattern, though in this case there was additional evidence (t(20)=1.99, p<.05) that Shallow Hits produced greater responses than Deep Hits as well (data not shown). Interestingly, a direct comparison of the inferior parietal region in Figure 3A and the superior (intra)parietal region in Figure 3B, in a 2 (inferior/superior) x 4 (trial-type) ANOVA, showed a reliable interaction between parietal region and trial-type F(2.52,47.9)=8.10, p<.001 (though this p-value may be biased by the different selection of these regions). This supports the proposal for distinct functions within left parietal cortex during recognition memory (see Discussion).

No regions showed a reliably greater response for Shallow Misses than Shallow Hits.

Shallow Misses versus Correct Rejections

Regions showing differential responses for Shallow Misses and Correct Rejections are shown in Table 7. The only region that showed a reduced response for Shallow Misses relative to Correct Rejections – the pattern of "repetition suppression" that has previously been associated with priming (Henson, 2003) – was in anterior cingulate; none of the expected regions (viz. those associated with perceptual processing, e.g, extrastriate cortex, Schacter & Buckner, 1998, or phonological/conceptual processing, e.g, left inferior prefrontal cortex, Wagner et al., 2000) showed reliable evidence for such repetition suppression.

A few regions showed greater responses to Shallow Misses than Correct Rejections. One of these, in right frontopolar cortex (BA 10), has previously been associated with episodic retrieval (Buckner & Wheeler, 2001; Fletcher & Henson, 2001; Lepage et al., 2000). This region also appeared to be the homologue of the left

frontopolar region identified by the Shallow Hits vs. Shallow Misses contrast (Figure 3B). Unlike its left homologue however, it showed greater responses for all studied words, regardless of the participant's old/new decision, than for correctly rejected new words (Figure 3C). Indeed, a 2x4 post hoc ANOVA on left and right frontopolar regions showed a reliable interaction between laterality and trial-type, $F(2.65,50.3)=3.63$, $p<.05$ (though again, this p-value may be biased by the different selection of the left and right regions).

Discussion

The present study provided some evidence in support of the distinction between different forms of explicit memory, namely recollection and familiarity, though little evidence for a further dissociable form of implicit memory, at least in terms of hemodynamic response reductions in regions previously associated with perceptual or conceptual priming. That is, when comparing correct recognition of deeply-studied items (Deep Hits) with correct recognition of shallowly-studied items (Shallow Hits) – a study manipulation that has been shown to disproportionately increase recollection (Yonelinas, 2002) – we found increased responses in a few regions expected on the basis of previous imaging studies, most notably left inferior parietal cortex. When comparing correct recognition of shallowly-studied items (Shallow Hits) with failed recognition of shallowly-studied items (Shallow Misses), we found increased responses in several other regions of interest, which in general showed little evidence of differences between Deep Hits and Shallow Hits. This is a pattern one might associate with a familiarity signal that was independent of recollection (Yonelinas, 2002; though see below). We failed to find any difference however, at least in regions expected from previous studies, between unstudied items that were correctly rejected (Correct Rejections) and shallowly-studied items that were incorrectly rejected (Shallow Misses), although such items might have been expected to show effects of prior study in the absence of conscious memory, i.e, implicit memory. Together, the pattern of responses across our four trial-types provided further insights on the functional properties of several brain regions

previously associated with recognition memory, including anterior medial temporal cortex.

Recollection and parietal cortex

Assuming for the moment that our subtractions gave pure measures of the three hypothetical types of memory (see below), our finding of activation of left inferior parietal gyrus in association with recollection is consistent with a number of previous imaging studies of recognition memory for words. For example, left inferior parietal gyrus showed greater responses for Remember than for Know judgments (Henson et al., 1999b; Eldridge et al., 2000; Wheeler & Buckner, 2004), and for correct rejection of similar words (recombinations) than for correct rejection of dissimilar words (McDermott et al., 2000); both situations where recollection would be expected. Similarly, right parietal cortex showed greater responses for correct than for incorrect retrieval of the spatial source of objects (Cansino et al., 2002). (Most of these studies also activated posterior cingulate in association with recollection, Rugg & Henson, 2002, which we were surprised not to see here.)

Furthermore, we found further evidence supporting a dissociation in the memory-related functions of different parts of parietal cortex (Herron et al., 2004; Wheeler & Buckner, 2004). A somewhat more medial region of left parietal cortex within the intraparietal sulcus (though extending to superior parietal lobule) showed greater responses to Deep and Shallow Hits than to Shallow Misses or Correct Rejections, but little difference between Deep and Shallow Hits. Indeed, we found a reliable interaction across trial-type between this region and the more lateral, inferior parietal region discussed above (which showed greater responses to Deep Hits than any of Shallow Hits, Shallow Misses or Correct Rejections; cf. Figure 3A and 3B). This interaction is highly consistent with the pattern of responses found by the Remember/Know studies of Henson et al (1999) and Wheeler and Buckner (2004), in which the lateral parietal region showed greater responses to Correct Remember than Correct Know judgments, and the intraparietal region showed similar responses to Correct Remember and Correct Know, but greater responses to both than to Correct

Rejections. Indeed, the concordance across studies between the MNI coordinates of the lateral region (-51 -57 +45 here; -57 -51 +39 in Henson et al., 1999b; -51 -51 +38 in Wheeler & Buckner, 2004) and of the intraparietal region (-30 -72 +51 and -30 -69 +36 here; -33 -60 +45 in Henson et al., 1999b; -39 -55 +36 in Wheeler & Buckner, 2004) is remarkable (see also Yonelinas et al., submitted, for a similar pattern across lateral and intraparietal regions, though see Dobbins et al., 2003, for a different pattern). Note that the regions we have called lateral parietal and intraparietal also differ in their superior and posterior extent; more precise anatomical localization is clearly needed (see Wheeler & Buckner, 2004, for further discussion).

While the lateral parietal responses would appear selective to recollection, the functional role of the intraparietal region is less clear. Though it would be associated with familiarity by the present operationalization, other evidence leads us to propose that it is more likely related to "target" effects, rather than memory effects. This is because a similar functional dissociation within left parietal cortex was found by Herron et al. (2004): Whereas an inferior parietal region showed greater responses to Hits than Correct Rejections (old-new effect) regardless of the ratio of old:new items, a more superior region showed an interaction between the old-new effect and the old:new ratio, with greater responses to Hits only when old items were the rarer items. The coordinates of this superior region (-39 -30 +54 and -33 -57 +60) are closer (in Euclidean terms) to those of the present intraparietal region than they are to the present lateral region. (Whether the inferior parietal region in Herron et al., 2004, that showed an old-new effect regardless of old:new ratio, which had peak coordinates -33 -72 +30, corresponds to the present lateral region is currently unclear.) Since participants in the Herron et al. (2004) study were informed of the ratio of old to new items prior to each session, the increased superior parietal response to the rarer items may reflect what participants' viewed as the targets. The nature of the more conventional recognition memory instructions, on the other hand, is such that participants are more likely to view old items as targets. This is likely to be the case in the present study, and hence this hypothesis is consistent with the basic pattern found

within the intraparietal region, namely greater responses to "old" decisions than to "new" decisions, regardless of study task or even study status. (This hypothesis may also explain the greater response to false alarms than correct rejections reported in this region by Wheeler and Buckner, 2003).

Prefrontal cortex and target effects

In addition to intraparietal cortex, two prefrontal regions showed greater responses to Shallow Hits than Shallow Misses, namely left frontopolar cortex (BA 10) and left middle frontal gyrus (BA 8/9; possibly corresponding to the posterior aspect of dorsolateral prefrontal cortex). Like the intraparietal region, the frontopolar region appeared to track participants' decisions ("old" judgments producing more activity than "new" judgments), regardless of study task or study status (Figure 3B). This region has been previously associated with recollection (Rugg & Henson, 2002), though the present pattern of responses is not consistent with this interpretation (see also Yonelinas et al., submitted). The more dorsolateral prefrontal region showed a similar pattern, though in this case there was additional evidence of greater responses to Shallow than Deep Hits. This region has previously been associated with retrieval monitoring (Henson et al., 1999a), the precise predictions of which are unclear in the present context, but which are at least not contested by the present response profile (e.g, the results would be consistent with the proposal that Shallow Hits were associated with less confident responding and required more monitoring; cf. Henson et al., 2000). However, both of these regions also showed an interaction between old-new effects and the old:new ratio in the Herron et al. (2004) study, suggesting that their responses may be better explained in terms of target effects than memory effects (though Rugg et al., 2003, found greater left frontopolar activity for source nontargets than correct rejections in an Exclusion task, participants in that study may have adopted the strategy of trying to detect old items prior to making a source decision, in which case any old item would have been treated as highly salient). We suspect that activation of these prefrontal regions depends more on the specific task demands than recognition success per se (Dobbins et al., 2003).

More unexpected was activation of a homologous region in right frontopolar cortex in the comparison of Shallow Misses and Correct Rejections. This region has also previously been associated with retrieval success (Rugg & Henson, 2002) and/or adoption of a state-related "retrieval mode" (Lepage et al., 2000). Neither of these hypotheses would appear to predict the present difference between new responses to studied items and new responses to unstudied items (Figure 3C). Moreover, this effect appeared to be lateralized, in that Shallow Misses were associated with different levels of response relative to Shallow Hits and Correct Rejections across the left and right frontopolar regions. Lateralization of frontopolar cortex during recognition memory has been reported previously (Herron et al., 2004), though a satisfactory explanation for this functional laterality remains to be established.

Familiarity and anterior MTL

While the above arguments indicate that the present operationalization of familiarity by Shallow Hits versus Shallow Misses may not have been sufficient to distinguish familiarity from other processes (such as those relating to target effects), at least one region in the present study showed a response consistent with what previous studies have suggested represents a familiarity signal. This was the anterior temporal cortex region identified as showing a relative response reduction for Hits compared with Correct Rejections. This region (albeit on the left rather than right) is close to that found in a meta-analysis by Henson et al. (2003) and most likely corresponds to perirhinal cortex. In that meta-analysis, we were unable to determine whether the relative deactivation to old items reflected familiarity or priming. We were hoping that the present study might do so, by allowing comparison of the response to Shallow Misses with those to Shallow Hits and Correct Rejections. If the deactivation reflected familiarity, one might expect Hits to produce smaller responses than both Misses and Correct Rejections. If, on the other hand, the deactivation reflected priming, one might expect both Hits and Misses to produce smaller responses than Correct Rejections. Unfortunately, the size of the response for Shallow Misses in the present study fell midway between that for Shallow Hits and that for Correct Rejections, with

no evidence that it differed reliably from either. A recent study using pictures by Weis et al. (2004) did find evidence for a smaller response to Hits than Misses in a somewhat more posterior/superior MTL region (-24 -20 -16). If this is the same region (see also Danckert et al., 2004), these other data suggest that deactivation of this region represents a familiarity signal that is used by participants to guide their old/new decisions. Indeed, if familiarity reflected a continuum of memory strength (Yonelinas, 2002), one might expect the same relative pattern of responses across Shallow Hits, Shallow Misses and Correct Rejections that was found in the present study: even though the level of familiarity for items that were missed was insufficient to attract an "old" response (given the participant's response criterion), it was likely to be higher than the familiarity of unstudied items that were correctly rejected. According to this argument, the same "intermediate" level of familiarity, elicited here by Shallow Misses, could just as easily have been associated with Hits, had participants employed a more liberal response criterion.

We note that in our meta-analysis, the anterior MTL region showed a deactivation relative to the interstimulus baseline for old (but not new) items. Though the estimated event-related response appeared greater than baseline in present study (Figure 2; baseline corresponding to zero), in none of the conditions was this significant. This is probably because the present study was designed to have maximal power to detect differences between event-types (by using a short, fixed SOA), and as a consequence had little power to estimate responses versus baseline (Josephs & Henson, 1999).

Implicit Memory

Repetition priming has previously been associated with a reduction in the hemodynamic response (repetition suppression) in regions responsible for processing a given stimulus in a given task (Schacter & Buckner, 1998; Henson, 2003). We failed to observe such reductions in any occipital, temporal or prefrontal regions presumed responsible for visual, lexical or semantic processing of words. There may be several reasons for this failure. The first may simply be lack of power (i.e, a null result). A

second relates to the fact that we had no behavioral measure of implicit memory, i.e,

priming. It could be, for example, that there was no difference in the fluency with

which Shallow Misses were processed relative to the fluency with which Correct

Rejections were processed. In other words, whenever studied items were processed

more fluently than unstudied items, this fluency was always attributed to the prior

study phase (Whittlesea & Williams, 2000), resulting in a feeling of familiarity and a

Hit rather than a Miss. However, this possibility would not explain why the previous

ERP study of Rugg et al. (1998), which we attempted to reproduce as closely as

possible, did find behavioral evidence of priming using a semantic decision task with

the same stimuli and, more importantly, found a distinct ERP correlate of implicit

memory using the same operationalization (an effect subsequently replicated by

Friedman, in press). It would be useful in this regard to examine False Alarms

(incorrect endorsement of unstudied items), which would be expected to have higher

familiarity than correct rejections, but unfortunately there were insufficient numbers

in the present study.

A third possible reason for our failure to find repetition suppression in

expected regions in association with Shallow Misses is that previous studies have

typically associated repetition suppression with (long-term) priming solely on the

basis that it was found in an indirect memory task (in contrast with the present direct

memory task). Few studies have convincingly ruled out possible contamination of the

indirect task by concurrent explicit memory (Henson, 2003). It therefore remains at

least logically possible that hemodynamic response reductions as manifest in indirect

tasks are a consequence of explicit memory. One exception to this possibility however

is a recent study by Schott et al. (submitted), who found repetition suppression in left

inferior temporal and left inferior prefrontal cortex for word-stems that were

completed with studied words that participants endorsed as unstudied (such items

were presumably primed in the absence of explicit memory). A fourth possibility is

that the explicit orientation of attention towards repeated (studied) items that is

engendered by a direct memory task potentiates responses sufficiently to 'swamp' the

repetition suppression associated with priming. This explanation was offered in a previous study to account for repetition suppression in fusiform/occipital regions for famous faces in an indirect memory task, but not in a direct memory task (Henson et al., 2002).

Encoding

The comparison of subsequent Deep Hits versus subsequent Shallow Hits at study revealed regions commonly associated with controlled semantic retrieval, including anterior/ventral left inferior frontal gyrus (Wagner et al., 2001). While we cannot unambiguously associate these activations with memory encoding, many of them have been associated with encoding in previous studies, particularly for semantic tasks with verbal material (e.g, Wagner et al., 1998; Otten et al., 2001; Baker et al., 2001; Davachi et al., 2001; Fletcher et al., 2003), and particularly for items subsequently recollected (Henson et al., 1999b; Davachi et al., 2003; Ranganath et al., 2003).

The comparison of subsequent Shallow Hits versus subsequent Shallow Misses can be more clearly associated with memory encoding. This comparison revealed activations within the inferior frontal sulcus, generally dorsal to those revealed by the comparison of subsequent Deep versus Shallow Hits (see also Baker et al., 2001; Davachi et al., 2001). That ventral aspects of the inferior frontal gyrus (i.e, excluding the small, dorsal region of overlap in Figure 1C) showed a depth of processing effect but not a subsequent memory effect under the shallow task is consistent with the task-by-encoding interaction in ventral inferior frontal gyrus reported by Fletcher et al (2003) and with the proposal that different regions support memory encoding in different tasks (Otten & Rugg, 2001a). Indeed, it is interesting to note that the pattern of subsequent memory activations under the present shallow task (in bilateral inferior frontal sulcus and bilateral inferior parietal cortex) resembles the pattern of subsequent memory _de_activations under a deep task reported by Otten and Rugg (2001b). This would suggest that the processes that help encoding under an orthographic task are actually the same as those that hinder encoding under a semantic

task. Some candidate processes might include processing of "perceptual", "item" or "externally-generated" information at the expense of "conceptual", "relational" or "internally-generated" information.

We failed to find any MTL regions that predicted subsequent memory under the orthographic task. Most studies that have reported subsequent memory effects in MTL using yes/no recognition have used semantic study tasks and restricted "subsequent Hits" to high confidence judgments (Wagner et al., 1998; Otten et al., 2001; Morcom et al., 2003), or used recall rather than recognition memory tasks (Strange et al., 2002). This suggests that MTL, particularly hippocampus, may only predict subsequent recollection, and not subsequent familiarity (see below).

We did find left anterior MTL activations, including hippocampus and parahippocampal cortex, for subsequent Deep Hits versus subsequent Shallow Hits. As mentioned above, this could simply reflect the additional semantic processing accorded to deeply studied items, or it could also reflect memory encoding processes that lead to subsequent recollection rather than subsequent familiarity. The latter is consistent with Davachi et al. (2003) and Ranganath et al (2003), who found that activity in hippocampus and posterior parahippocampal cortex predicted correct subsequent source retrieval, but not subsequent item memory (see Kensinger et al., 2003, for similar conclusions). Davachi et al. (2003) and Ranganath et al (2003) also reported that activity in perirhinal cortex / anterior parahippocampal cortex predicted subsequent item recognition regardless of source retrieval (a pattern one might interpret as subsequent familiarity in the absence of recollection). This is less consistent with the absence of a subsequent memory effect, yet presence of a depth of processing effect, that we found in perirhinal cortex (Figure 2).

Another interesting observation concerns the increased response of bilateral posterior parahippocampal cortices for subsequent Deep versus Shallow Hits, with little difference between Shallow Hits and Shallow Misses, and the increased response of more posterior, bilateral fusiform cortices for subsequent Shallow Hits versus Shallow Misses, with little apparent difference between Deep Hits and Shallow Hits

(cf. Figure 1A and 1B). Whether this apparent difference between parahippocampal and fusiform cortices reflects a dissociation between semantic processing and memory encoding, or differences between encoding processes leading to recollection and those leading to familiarity, it highlights an important functional-anatomical dissociation to be investigated further.

Other Issues

There are several factors that may have confounded our operationalizations of recollection, familiarity and priming. Firstly, there may have been incidental semantic processing of some items that were cued for orthographic decisions at Study. Though this potential confound would not affect the activations that were found when comparing Deep versus Shallow Hits at test (since Deep Hits would still be likely to produce a greater proportion of items eliciting recollection), it may have contributed to a failure to find correlates of recollection in other brain regions. Incidental semantic processing might have also meant that recollection contributed to the differences between Shallow Hits and Shallow Misses. One reason to doubt this potential confound however is that there was little evidence of a difference between subsequent Shallow Hits and subsequent Shallow Misses in the ventral regions of left inferior frontal gyrus that have been associated with controlled semantic retrieval (Wagner et al, 2001).

A second possible confound is that semantic encoding may increase the level of familiarity, as well as probability of recollection, relative to orthographic processing. Indeed, averaging across the 17 studies reviewed by Yonelinas (2002), deep encoding increased the estimates of both recollection and familiarity, though the mean increase in recollection (R=.28) was higher than the mean increase in familiarity (F=.16). Thus, some brain regions more active for Deep Hits than Shallow Hits may have reflected higher levels of familiarity rather than recollection. However, for the lateral (inferior) parietal region at least, the "step-like" pattern of differences in activity over Deep Hits, Shallow Hits and Shallow Misses (Figure 3A) is difficult to explain solely in terms of a continuum of familiarity (Yonelinas, 2002).

Finally, as already noted, our operationalization of priming by the contrast of Shallow Misses versus Correct Rejections may have included a contribution from familiarity that, while greater for Misses than Correct Rejections, did not exceed the response criterion. Thus some regions identified by this contrast, like right frontopolar cortex, might have been responding to sub-criterion levels of familiarity (though again, the step-like pattern in this particular region – see Figure 3C – is difficult to explain in terms of a continuum of familiarity).

Conclusion

To our knowledge, no single imaging study has yet convincingly dissociated recollection, familiarity and implicit memory in terms of their functional-anatomical correlates. This is important because the evidence from behavioral and neuropsychological studies for these distinctions is still controversial. Though the present study failed to provide unambiguous dissociations in this respect, it represents an important step towards this goal, highlighting several candidate brain regions.

Materials and Methods

Participants

Twenty-two volunteers gave written consent to participate in the study (6 men), aged 18-34, all right-handed. All volunteers reported themselves to be in good health, with no history of neurological illness. The study was of the type approved by university ethics committees (references: UCL/UCLH 99/0048, NH/ION 00/N031).

Materials

The critical stimuli consisted of 348 concrete nouns between 4 and 9 letters in length and of a low to medium frequency of occurrence. The words were randomly assigned to 3 groups of 116. Each group was used to construct a study list of 34 words to be studied deeply, 34 words to be studied shallowly, plus 4 initial fillers, and a test list of the 68 studied words plus 34 unstudied words and 10 initial fillers. Across

participants, each word served approximately equally often as a deeply-studied, shallowly-studied or unstudied item.

Procedure

For study lists, words were presented for 500ms with a stimulus onset asynchrony (SOA) of 5400ms. Each word was preceded for 2100ms by a cue (a '+' or 'o' symbol) which told participants whether to perform the deep or shallow task on the subsequent word. For the deep task, participants decided whether the word was related to a living or non-living thing; for the shallow task, participants decided whether the first and last letters of the word were in alphabetical order (responding 'no' if the first and last letters were identical). The type of cue was permuted randomly. Participants' "yes" or "no" responses were made by key presses using the index finger of their left or of their right hand.

For test lists, words were presented for 500ms with an SOA of 3240ms. Participants were instructed to respond whether they had seen each word in the previous study list, as quickly and as accurately as possible. There was an interval of approximately 2 minutes between study and test, during which participants counted backwards in threes (to clear their short-term memory). The assignment of response keys to left/right hands was counterbalanced over participants.

fMRI Acquisition

A 1.5T Sonata system (Siemens, Erlangen, Germany) was used to acquire 24 T2*-weighted transverse echoplanar (EPI) images (64x64 $3x3mm^2$ pixels, TE=50ms) per volume, with blood oxygenation level dependent (BOLD) contrast. EPIs comprised 3mm-thick axial slices taken every 4.5mm, acquired sequentially in a descending direction. Three study sessions and three test sessions were acquired, 175 scans for study, 185 scans for test. Volumes were collected continuously with a repetition time (TR) of 2.16s. The first 5 volumes per session were discarded to allow for equilibration effects. The ratio of SOA to TR ensured that the impulse response was sampled every 1.08s (over trials).

Behavioral Analysis

Test trials with RTs less than 200ms or greater than the SOA (3240ms) were marked as invalid. For trials with multiple responses, the last response was taken (though in the fMRI analyses, these trials were coded as invalid trials, to covary out atypical response-related activity). Trials were sorted into four conditions of interest: 1) items studied deeply and recognized ("deep hits"), 2) items studied shallowly and recognized ("shallow hits"), 3) items studied shallowly but not recognized ("shallow misses"), 4) items not studied and not recognized ("correct rejections"), and three conditions of no interest: 5) items not studied but recognized ("false alarms"), 6) fillers plus items studied deeply but not recognized, and 7) invalid trials.

Study trials were sorted similarly, being classified according to decisions in the subsequent test phase: 1) deep hits, 2) shallow hits, 3) shallow misses, 4) fillers plus deep misses and 5) invalid trials.

Following Rugg et al. (1998), we imposed a requirement of more than 16 events of each event-type of interest (at both study and test), which meant excluding two participants, leaving 20 participants for all statistical comparisons.

efMRI Analysis

Analysis of the fMRI data was performed with SPM2 (http://www.fil.ion.ucl.ac.uk/spm). All volumes were coregistered to the first volume, and unwarped to allow for interactions between EPI distortions and participant movement (Andersson et al., 2001). Scans in which the mean or variance of the difference between one or more slices and those in the previous scan exceeded 5 times the standard deviation of such differences over all scans per session were marked as outliers (to be modeled separately; see below). The data in each slice were interpolated in time to match the acquisition time of the middle slice. Spatial normalization parameters were estimated by warping each participant's mean EPI to a standard EPI template based in Talairach space (Ashburner & Friston, 1999). Normalized EPI images were resliced to 3x3x3mm voxels and smoothed with an isotropic 8mm FWHM Gaussian kernel (final estimated smoothness was $10x10x10mm^3$ FWHM). The timeseries in each voxel was highpass-filtered to 1/128

Hz and scaled to a grand mean of 100, averaged over all voxels and scans within a
session.

Statistical analysis was performed in two stages (Penny, 2004). In the first
stage, neural activity was modeled by a delta function at stimulus onset. The ensuing
BOLD response was modeled by convolving these delta functions with a canonical
hemodynamic response function (HRF, Friston et al., 1998). The resulting
timecourses were downsampled at the midpoint of each scan (corresponding to the
middle slice) to form covariates in a General Linear Model. Covariates were modeled
for each condition (see Behavioral Analysis above), plus separate covariates for each
outlier scan (consisting of a single delta function) and a single covariate representing
the mean (constant) over scans. Temporal autocorrelation of the errors was
accommodated by an AR(1) model, the parameters of which represent hyper-
parameters governing the nonsphericity of the error covariance, and which were
estimated together with the parameters for each covariate using Restricted Maximum
Likelihood (Friston et al., 2002).

Contrasts of parameter estimates comprised the data for the second-stage
analyses, which treated participants as a random effect. SPMs were thresholded for 5
or more contiguous voxels surviving $p < .001$. The maxima were localized on a
normalized mean EPI across participants. Stereotactic coordinates correspond to the
standard Montreal Neurological Institute brain. These coordinates bear a close, but not
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Table 1. Mean number of trials (max=102) and mean of median Reaction Time
(RT/ms) at Study and at Test for each condition of interest, together with range or
standard deviation (SD). Mean number of false alarms = 14 (range = 2-40). N=20
participants (two participants with 16 or less Shallow Misses were removed).

	Deep Hit	Shallow Hit	Shallow Miss	Correct Rejection
Number (Range)	91 (73-98)	64 (37-82)	38 (18-63)	88 (60-98)
RT Test (SD)	858 (86)	970 (161)	1155 (205)	975 (145)
RT Study (SD)	1236 (215)	1532 (249)	1547 (226)	-

Table 2. Regions showing depth of processing effects at study (subsequent Deep Hit versus subsequent Shallow Hit). L=left, R=right, B=bilateral, BA=Brodmann Area.

Region	L/R	Size (cm^3)	BA	MNI Coordinates			Z-score
				x	y	z	
Subs. Deep Hit > Subs. Shall. Hit							
Medial/Superior frontal gyrus	B	17.8	10	-3	+60	+21	4.52
			10	0	+51	-3	4.36
			8	-6	+45	+51	4.87
Superior frontal gyrus	R	0.14	8	+15	+42	+51	3.84
Middle frontal gyrus	R	0.14	47	+54	+42	-3	3.98
Inferior frontal gyrus	L	4.40	47	-42	+27	-18	4.88
			45	-48	+27	+12	4.23
	R	0.24	47	+48	+27	-12	3.70
Temporal pole	L	1.78	21/38	-42	+9	-30	5.02
				-36	+21	-33	3.34
	R	0.86	21/38	+42	+9	-36	4.68
Anterior inferior temporal gyrus	L	0.43	20	-33	-3	-39	4.51
Anterior medial temporal	L	1.13	34/35	-30	+3	-21	3.37
				-21	-6	-30	4.68
				-15	-12	-21	3.62
Parahippocampal gyrus	L	0.94	36	-30	-30	-24	4.50
	R	1.62	36	+27	-33	-21	4.99
Middle temporal gyrus	L	0.16	21	-60	-36	-9	3.55
Posterior cingulate/Precuneus	L	0.54	30/31	-6	-51	+30	3.76
Superior temporal/angular gyrus	L	0.70	39	-48	-63	+27	3.78
Cuneus	R	0.19	18	+12	-102	+18	3.57

Table 3. Regions showing subsequent memory effects at study (subsequent Shallow Hit versus subsequent Shallow Miss). L=left, R=right, BA=Brodmann Area.

Region	L/R	Size (cm^3)	BA	MNI Coordinates			Z-score
				x	y	z	
Subs. Shall. Hit > Subs. Shall. Miss							
Inferior frontal sulcus /	L	11.3	11	-42	+42	+3	5.05
Middle frontal gyrus			46	-48	+33	+21	4.00
			45	-57	+21	+21	4.04
			9	-45	+15	+30	3.83
			6/9	-39	0	+30	4.37
	R	1.11	9/46	+54	+33	+27	3.71
	R	0.27	46	+45	+30	+12	3.43
	R	0.19	8	+30	+12	+45	3.49
	R	0.91	6/9	+42	+3	+27	4.26
Caudate	L	0.16	-	-15	+6	+18	3.51
Insula	R	0.43	38	+36	+9	-27	3.61
			20	+45	-3	-21	3.32
Thalamus	L	0.19	-	-6	-6	+18	3.39
Fusiform gyrus	L	0.95	37	-48	-48	-12	3.81
	R	0.19	37	+51	-45	-15	3.23
Inferior parietal /	L	3.05	40	-57	-51	+39	4.00
Angular gyrus			39	-27	-63	+36	4.17
			39	-51	-69	+33	3.49
	R	0.62	40	+51	-54	+48	3.40

Table 4. Regions showing differential responses to Hits (Deep+Shallow) versus

Correct Rejections at Test. L=left, R=right, B=bilateral, BA=Brodmann Area.

Region	L/R	Size (cm^3)	BA	MNI Coordinates			Z-score
				x	y	z	
Hit > Correct Rejection							
Anterior middle frontal gyrus	L	0.40	10	-36	+48	+9	3.49
Cingulate sulcus	B	1.43	6	-6	+30	+42	4.68
Posterior inferior frontal sulcus	L	2.51	9	-45	+30	+39	3.72
			9	-33	+12	+39	4.00
Inferior frontal gyrus	L	0.51	47	-33	+24	-9	3.65
Middle frontal gyrus	L	0.43	6/8	-30	+9	+57	3.93
	R	0.81	6/8	+42	+9	+48	3.60
Caudate	R	0.86	-	+9	+15	-6	3.65
	R	0.14	-	+12	+6	+18	3.23
Middle temporal gyrus	R	1.00	21	+63	-39	-9	4.55
Precuneus/posterior cingulate	B	26.4	31	-3	-39	+36	4.61
			30	3	-45	+21	4.57
			7	-3	-69	+33	5.44
			7	+6	-78	+54	4.25
Inferior parietal/Supramarginal	L	1.43	40	-48	-42	+45	3.75
			40	-54	-54	+33	3.85
Intraparietal sulcus	L	11.0	40	-36	-60	+45	4.48
			7	-36	-57	+54	4.39
			19	-36	-72	+39	4.52
	R	7.61	40	+45	-48	+54	4.31
			7	+21	-63	+45	4.05
			19	+33	-69	+42	4.25
Cuneus	L	0.32	23	-9	-75	+6	3.45
Lingual gyrus, posterior	B	7.61	18	0	-96	-6	4.04
Correct Rejection > Hit							
Anterior medial temporal (uncus)	L	0.22	36	-30	0	-33	3.52

Table 5. Regions showing differential responses to Deep Hits versus Shallow Hits at
Test. L=left, R=right, BA=Brodmann Area.

Region	L/R	Size (cm^3)	BA	MNI Coordinates			Z-score
				x	y	z	
Deep Hit > Shallow Hit							
Middle temporal gyrus	L	0.49	21	-66	-21	-6	3.77
Inferior parietal lobule	L	0.38	40	-51	-57	+45	3.71
			39	-51	-66	+42	3.41
Supramarginal gyrus	R	0.14	40	+51	-51	+21	3.19
Middle temporal gyrus	L	0.30	19	-54	-66	+15	3.37
Shallow Hit > Deep Hit							
Anterior cingulate	L	0.16	32	-3	+21	+39	3.51
Middle occipital gyrus	L	0.19	19	-51	-60	-9	3.30

Table 6. Regions showing greater responses to Shallow Hits versus Shallow Misses
(no regions showed greater responses to Shallow Misses than Shallow Hits). L=left,
R=right, BA=Brodmann Area.

Region	L/R	Size (cm³)	BA	MNI Coordinates			Z-score
				x	y	z	
Shallow Hit > Shallow Miss							
Frontopolar (superior frontal)	L	0.30	10	-18	+63	+9	4.00
Middle frontal gyrus	L	0.73	8/9	-48	+12	+42	4.30
Intraparietal sulcus	L	5.43	40	-42	-54	+60	4.10
			19	-30	-69	+36	3.45
			7	-30	-72	+51	4.85
	R	1.16	19	+30	-69	+36	5.38
Precuneus	L	0.38	7/31	-15	-60	+21	3.81
	R	0.70	7/31	+12	-66	+36	3.82

Table 7. Regions showing greater responses to Shallow Misses versus Correct
Rejections. L=left, R=right, B=bilateral, BA=Brodmann Area.

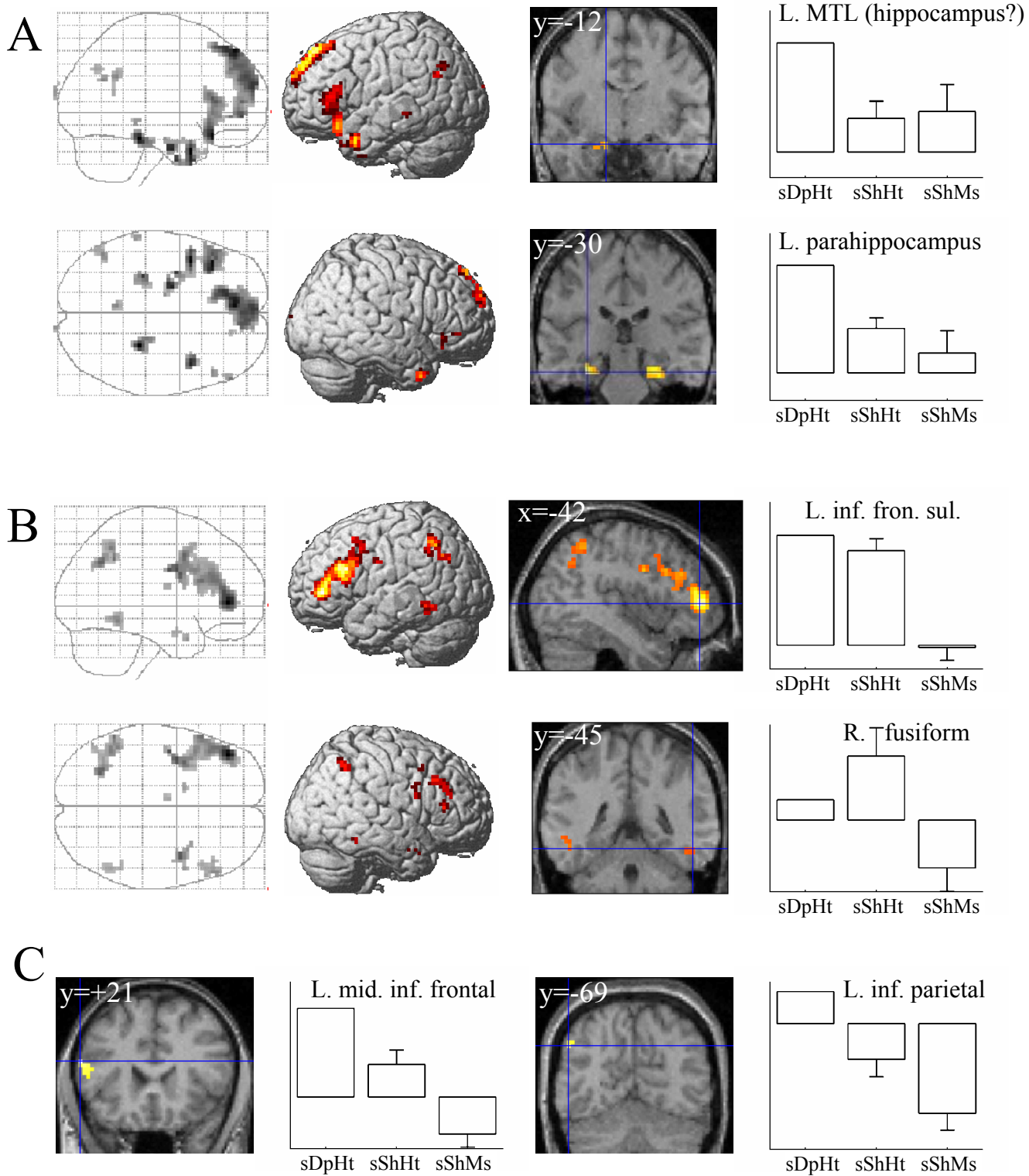| Region	L/R	Size (cm^3)	BA	MNI Coordinates			Z-score
				x	y	z	
Shallow Miss > Correct Rejection							
Frontopolar (superior frontal)	R	0.14	10	+24	+60	+12	4.43
Medial superior frontal gyrus	R	0.38	8	+3	+18	+54	3.54
Precentral gyrus	L	0.24	6	-42	-9	+45	3.53
Lingual gyrus	L	0.40	18	-9	-81	-9	4.34
Correct Rejection > Shallow Miss							
Anterior cingulate	B	0.22	24	0	+27	+15	3.84

Figure 1

Results at Study: Regions showing greater responses (p<.001 uncorrected, 5 contiguous voxels) for A) subsequent Deep Hits versus subsequent Shallow Hits and B) subsequent Shallow Hits versus subsequent Shallow Misses, C) both A and B. Leftmost column shows Maximal Intensity Projections (MIPs). Second column shows same data rendered onto surface of a canonical brain (deep activations not shown). Third column shows sections through a normalized T1 image of a randomly selected participant that highlight regions of interest, viz. left MTL, most likely including hippocampus, and bilateral parahippocampal gyri (in A), left inferior frontal sulcus and bilateral fusiform (in B), and left mid inferior frontal gyrus and left inferior parietal/angular gyrus (in C). Rightmost column shows size of best-fitting canonical HRF for subsequent Deep Hits (sDpHt), subsequent Shallow Hits (sShHt) and subsequent Shallow Misses (sShMs) from maxima of regions indicated by cross-hair in third column (scale arbitrary; zero not estimated reliably in present design). Error bars (from left to right) show standard error of difference between sDpHt vs. sShHt, and sShHt vs. sShMs.
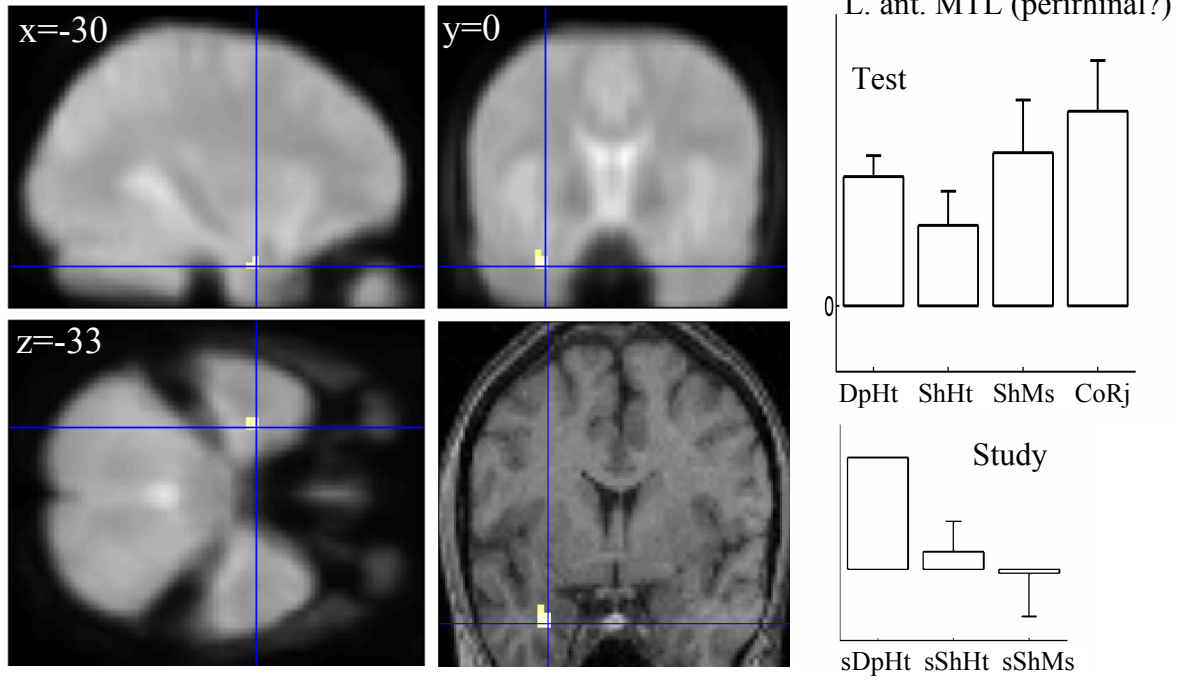

Figure 2

Left anterior MTL region showing deactivation for Hits relative to Correct Rejections (CoRj) at Test, most likely in perirhinal cortex. Orthogonal sections on left and upper right derive from mean normalized EPI over participants; section in lower right is from normalized T1 image of a randomly selected participant. Plots show size of best-fitting canonical HRF for each condition at Test (upper) and at Study (lower). Error bars (from left to right) at Test show standard error of difference between Hits vs. CoRj, DpHt vs. ShHt, ShHt vs. ShMs, and ShMs vs. CoRj; error bars at Study show standard error of difference between sDpHt vs. sShHt, and sShHt vs. sShMs; see Figure 1 legend for more details
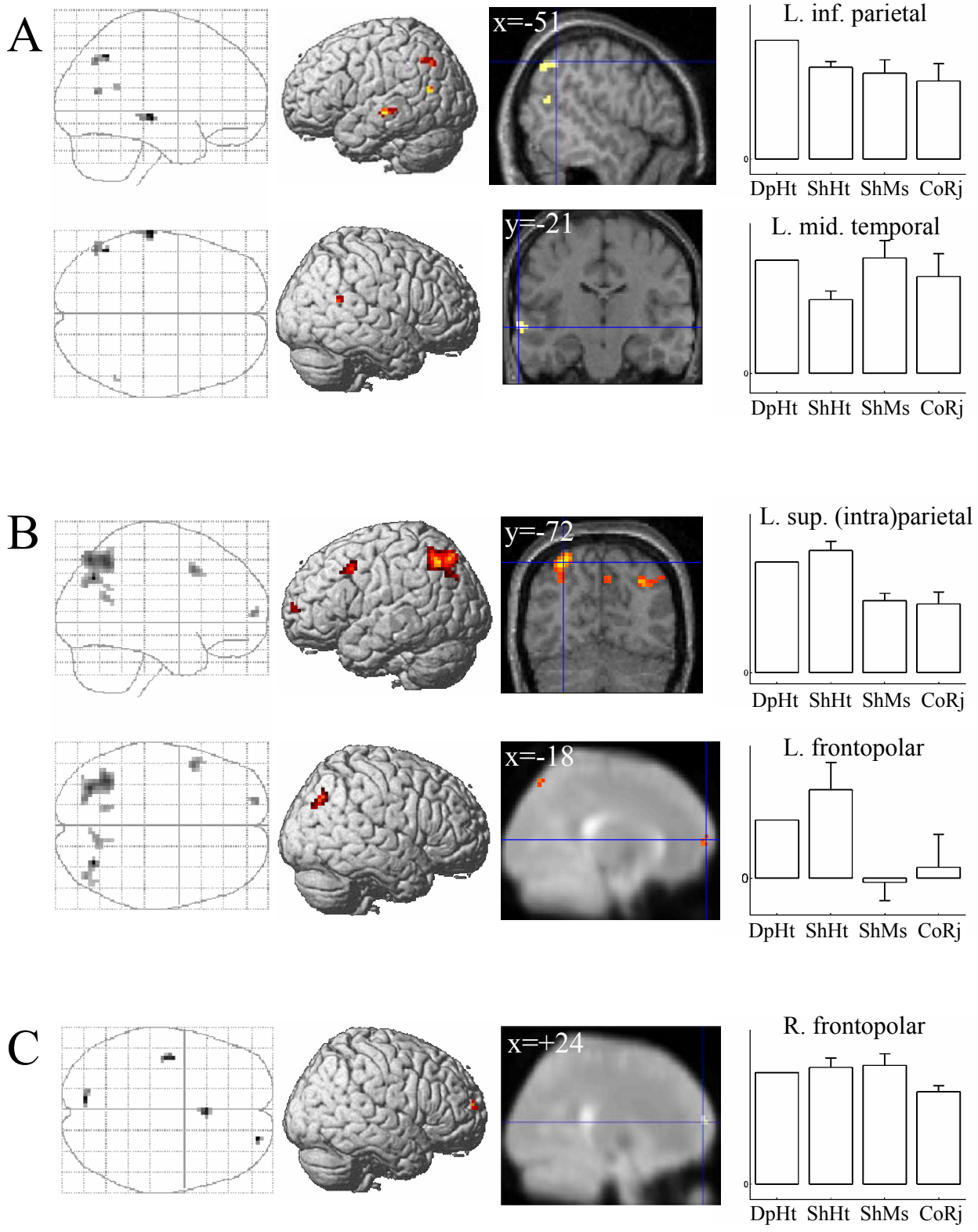
Figure 3

Results at Test: Regions showing greater responses for A) Deep Hits versus

Shallow Hits and B) Shallow Hits versus Shallow Misses, C) Shallow Misses versus

Correct Rejections. Regions shown in sections in third column are left inferior

parietal/angular gyrus and left middle temporal (in A), left superior (intra)parietal and

left frontopolar (in B) and right frontopolar (in C). Some sections in panel B and C

come from mean normalized EPI rather than structural, to illustrate activation location

relative to EPI susceptibility effects. Error bars (from left to right) show standard error

of difference between DpHt vs. ShHt, ShHt vs. ShMs, and ShMs vs. CoRj; see Figure

1 legend for more details.

A

L. MTL (hippocampus?)

y=-12

sDpHt   sShHt   sShMs

L. parahippocampus

y=-30

sDpHt   sShHt   sShMs

B

L. inf. fron. sul.

x=-42

sDpHt   sShHt   sShMs

R. fusiform

y=-45

sDpHt   sShHt   sShMs

C

y=+21

L. mid. inf. frontal

sDpHt   sShHt   sShMs

y=-69

L. inf. parietal

sDpHt   sShHt   sShMs

Henson et al, Figure 1

x=-30   y=0

z=-33

L. ant. MTL (perirhinal?)

Test

0

DpHt   ShHt   ShMs   CoRj

Study

sDpHt sShHt sShMs

Henson et al, Figure 2

A

L. inf. parietal

x=-51

DpHt ShHt ShMs CoRj

L. mid. temporal

y=-21

DpHt ShHt ShMs CoRj

B

L. sup. (intra)parietal

y=-72

DpHt ShHt ShMs CoRj

L. frontopolar

x=-18

DpHt ShHt ShMs CoRj

C

R. frontopolar

x=+24

DpHt ShHt ShMs CoRj

Henson et al, Figure 3