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Item- and Task-Level Processes in Left Inferior Prefrontal Cortex: Positive and Negative Correlates of Encoding

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Abstract

Activity in left inferior prefrontal cortex (LIPC) is often thought to reflect processes that support episodic encoding. Functional magnetic resonance imaging (fMRI) was used to test whether processes subserved by LIPC could be negatively related to subsequent memory performance. Specifically, the current experiment explicitly tested the hypothesis that LIPC processing would positively impact encoding when primarily focused towards specific target items (item-level processing), whereas it would negatively impact encoding when primarily focused on the retrieval and instantiation of the current task instructions (task-level processing). Two methods were used in order to identify regions that were sensitive to the two types of processes: a block-level manipulation of encoding task that influenced subsequent memory, and a back-sort procedure. LIPC was sensitive to item- and task- level processing, but *not* in a way that always facilitates encoding. LIPC was more active for subsequently remembered words than subsequently forgotten words, but it was also more active in a task that emphasized task-level processing relative to a task that emphasized item-level processing, despite the fact that this former condition led to poorer subsequent memory performance. This pattern indicates that processes subserved by LIPC are not always positively correlated with episodic encoding. Rather, LIPC processes can support both the controlled semantic processing of items and the controlled retrieval of the relevant semantic task context. When devoted to the latter, the diversion of LIPC processes to the task level can have a negative consequence for item-level analysis and encoding.

Introduction

Neuroimaging provides a tool that allows researchers to investigate the neurocognitive processes that support episodic encoding. Over the past 10 years, numerous studies have provided evidence that a network of regions is involved in successful encoding, including regions in inferior prefrontal cortex, medial temporal lobes, and fusiform gyrus (Buckner et al., 1999; Buckner and Wheeler, 2001). The first neuroimaging studies that investigated encoding processes used blocked designs in which experimenters manipulated factors known to influence later recognition performance and found that activity in a set of regions co-varied with such manipulations (Demb et al., 1995; Fletcher et al., 1995; Gabrieli et al., 1996; Kapur et al., 1994; Shallice et al., 1994; Wagner et al., 1998). In particular, these studies identified prefrontal and medial temporal regions that displayed a positive correlation between the magnitude of their hemodynamic response and factors that support later memory performance. More recently, methodological advances have allowed experimenters to investigate the relationship between activity during encoding and subsequent memory on a trial-by-trial basis, while holding the encoding task constant (for review, see Paller and Wagner, 2002). Specifically, event-related fMRI designs have been used to contrast the processing of items that are subsequently remembered to those that are subsequently forgotten (Brewer et al., 1998; Wagner et al., 1998). Across studies, these two methodologies tend to converge: regions that positively covary with blocked manipulations of encoding also tend to be more active during the processing of stimuli that are subsequently remembered.

One of the most frequently identified regions that is positively correlated with later recognition is left inferior prefrontal cortex (LIPC). This region tends to be more active under task conditions that support more effective encoding, such as making semantic judgments

compared (e.g., abstract/concrete) to non-semantic judgments (e.g., letter case) about words (Baker et al., 2001; Kapur et al., 1994; Otten et al., 2001; Wagner et al., 1998), or when processing items under full attention compared to divided attention (Anderson et al., 2000; Iidaka et al., 2000; Kensinger et al., 2003; Shallice et al., 1994). Further, LIPC shows sensitivity at the item level, as it tends to demonstrate a larger event-related response during the processing of words that are subsequently remembered relative to words that are subsequently forgotten (e.g. Clark and Wagner, 2003; Kirchhoff et al., 2000; Wagner et al., 1998). Additionally, there have been three direct tests of this convergent pattern in the same participants. All three studies found regions in LIPC that displayed larger responses during both semantic compared to non-semantic tasks and the processing of subsequently-remembered compared to subsequently-forgotten items (Baker et al., 2001; Fletcher et al., in press; Otten et al., 2001). Thus, extant data suggest that LIPC computations, when devoted to the processing of an item, positively impact encoding of the item: LIPC is more active under conditions that lead to better subsequent recognition performance relative to conditions that lead to poorer subsequent recognition, and LIPC is more active during the processing of words that are subsequently remembered than of words that are subsequently forgotten.

Although there is substantial data suggesting that activity in LIPC is positively correlated with subsequent memory performance, the mechanisms underlying this relationship are still not well understood. One hypothesis suggests that LIPC is involved in the biasing (i.e. sculpting) of semantic space, supporting the retrieval of semantic knowledge about items (Fletcher et al., 2000; Wagner et al., 2001). Under this hypothesis, LIPC serves to emphasize the task-relevant semantic features of a stimulus relative to task-irrelevant semantic features. This hypothesis suggests that LIPC is involved in the controlled retrieval of semantic information (Wagner et al., 2001). This

type of processing could account for the previously stated subsequent memory effects by adding the corollary that controlled retrieval of semantic information typically facilitates encoding, perhaps by providing a more elaborated episodic trace. Increases in activity in response to block level manipulations of encoding (e.g. semantic vs. non-semantic judgments), may be due to the nature of the tasks: semantic judgments demand the biasing of semantic space more than do non-semantic judgments. In order to account for the event-related effects, one needs only to assert that there is a variable demand on the controlled retrieval process. This variability would produce trial-by-trial differences in the amount of item-level semantic retrieval and elaboration. To the extent that semantic retrieval and elaboration facilitate encoding, those items with greater elaboration (and therefore greater LIPC activity) will be more likely to be recognized during test (e.g. Kapur et al., 1994; Wagner et al., 2000).

The hypothesis that LIPC biases or sculpts semantic space to support the retrieval of task-congruent item level knowledge inline with current task-demands rests on the often implicit assumption that LIPC mechanisms also serve to represent the semantic context corresponding to the current task instructions (e.g. Badre and Wagner, 2002). To the extent that this assumption is true, one might expect LIPC mechanisms to also play a role in retrieving or instantiating the target semantic context. Some recent evidence lends initial support for this assumption. Specifically, Bunge and colleagues (in press) used a trial-by-trial cueing paradigm in which participants were instructed to perform either a match-to-sample, nonmatch-to-sample, or go-left/go-right task on any given trial. They found that LIPC responded to a cue instructing participants to retrieve the task context of the current trial, which was to then guide subsequent item-level processing. Moreover, the complexity of the task instructions influenced the magnitude of the LIPC response, such that the response was larger during the retrieval of more conceptually

complex task representations (match and nonmatch to sample) relative to the simple task (go-left/go-right). This sensitivity to task or rule-complexity was maintained over a delay period between the offset of the task-cue and the onset of the target stimuli. Together, these data suggest that LIPC is involved in the retrieval and maintenance of the appropriate task/rule representations.

The preceding data suggest that activity in LIPC does not solely reflect the biasing of item-specific semantic knowledge (item-level processing), but also reflects the retrieval and instantiation of the appropriate semantic task representation that is required to perform this biasing (task-level processing). Importantly, to the extent that the processes that retrieve and instantiate the semantic context are the same as those that subsequently bias the semantic space associated with an item, one might predict that LIPC task-level and item-level computations can interfere with one another. Accordingly, whereas the item-level processing performed by LIPC is typically positively correlated with subsequent memory, task-level processing in LIPC may *negatively* impact subsequent memory when such processing is performed at the expense of item-level computations. That is, when task-level processing takes resources away from item-level processing, one would predict a negative correlation between LIPC activation and subsequent memory.

The current experiment provided an explicit test of this hypothesis. In particular, this study examined the effect of a semantic task-switching manipulation on activity dynamics in LIPC and subsequent memory performance. Behavioral performance and activity dynamics on trials in which the to-be-performed task was the same on every trial in the block (SINGLE-TASK) were compared to that of trials in which the to-be-performed task changed randomly on every trial in the block (TASK-SWITCHING). The task-switching block should place greater

demands on the retrieval and instantiation of the task-relevant semantic context (e.g. task-level processes) because participants had to consistently monitor and comprehend which task was to be performed on each trial.

In as much as the task-switching manipulation influenced the degree of task-level processing required on a given trial, it was expected that LIPC would elicit greater responses during trials embedded in a task-switching as opposed to a single-task block. Further, to the extent that this task-level processing is in competition with item-level processing, this increase in LIPC activity should be negatively, rather than positively, related to subsequent memory performance. Finally, it was anticipated that the block manipulation would not interact with the standard item-level effect, such that subsequently remembered words were predicted to elicit greater activity in LIPC relative to subsequently forgotten words. This prediction follows from the assumption that, within a block, the demand on task-level processes should be relatively constant, and therefore one should observe only trial-by-trial fluctuations in item-level processes.

It is important to note that the above detailed set of predictions is not the only set that one could propose. A priori, one might make the opposite prediction, namely that the added context of multiple semantic tasks would enrich the encoded representation, and might further facilitate the distinctiveness of item encoding and thus reduce interference/competition at retrieval (by minimizing cue overload). As such, this alternative perspective would predict that LIPC activity would remain positively correlated with subsequent memory performance at the item-level, and that subsequent memory performance would also be superior for words processed in the task-switching condition relative to the single-task condition.

A secondary goal of the study was to examine the effect of task-switching on brain regions that tend to be negatively correlated with encoding under standard conditions. In

particular, regions within medial parietal cortex / precuneus were also of interest because they have been consistently detected within the context of negative correlates of encoding (Otten and Rugg, 2001; Wagner and Davachi, 2001), and it was anticipated that the blocked manipulation would contribute additional insights regarding these subsequent forgetting effects.

These questions were examined within the context of a previously reported study (see Braver et al., in press). The study was originally designed to directly examine the effect of task-switching on behavioral performance and brain activity. However, an interest in encoding processes during task-switching prompted the inclusion of a surprise recognition test outside of the scanner. The present paper examines the relationship between activity during single-task and task-switching blocks and performance on this subsequent memory test.

Methods

Participants. 13 right-handed participants with no evidence of neurological compromise participated in this study. Participants were eight males and five females with a mean age of 21 years (range: 19-26 years). Participants gave informed consent per guidelines set by the Washington University Medical Center Human Studies Committee and were paid $25 for each hour of participation.

Behavioral Tasks. Participants performed two semantic classification tasks with words under single-task or task-switching conditions. One classification task, LRG-SML, required a decision as to whether the target word described an object larger or smaller than a standard computer monitor. The other task, MAN-NAT, required a decision as to whether the referent was man-made or natural. For both tasks, a task cue appeared prior to the target word and signaled the classification judgment to be made (LRG-SML or MAN-NAT). In the single-task condition, only one of the two tasks was performed during the entire block; the task-cue information was the

same on each trial and could therefore be ignored after the first trial. In the task-switching condition, the task cue (and therefore the relevant classification task) varied randomly from trial to trial. Thus, the task-switching condition induced an additional attentional load, because the random task cueing required the participants to constantly monitor and comprehend the cue information, thus retrieving or instantiating the target semantic context on each trial. Moreover, participants may have further had to maintain the accessibility of both task sets across trials, in order that the semantic contexts could be easily instantiated (Fagot, 1994; Pashler, 2000; Rogers and Monsell, 1995). All words varied on both the MAN-NAT and LRG-SML dimensions, with each possible combination presented with equal frequency. The word list assigned to each task condition (single-task vs. task-switching) was counterbalanced across participants.

Words were presented centrally on a visual display, in 36-point Helvetica font. Words were taken from standardized lists of concrete nouns. All words were 3-7 letters in length and consisted of one or two syllables. Participants responded to stimuli by pressing one of two buttons on a hand-held response box with either the index or middle finger of the right hand. The stimulus-response mappings were counterbalanced across participants. Within each trial, the timing and sequence of events were as follows. First, the task cue was presented for 750 ms, followed by a 1750 ms delay. Next, the target word was presented for 2000 ms, during which responses were recorded. Participants were instructed to make a classification decision as quickly and accurately as possible following onset of the target, and to indicate the nature of this decision with a button press. Next, a variable ITI (500-5500 ms) occurred to allow for estimation of the event-related hemodynamic response, as described below. Participants performed two repetitions of each of the single-task and task-switching conditions in separate scanning runs. For the single-

task condition, one run was performed of each classification task (MAN-NAT, LRG-SML). Each run consisted of 40 trials. Thus, there were 80 single-task trials and 80 task-switching trials.

Prior to the scanning session, participants were given instructions and practice for all tasks to be performed. During practice trials, the experimenter answered any further questions, validated that the instructions were understood, and ensured that the tasks were performed appropriately and with a reasonably high level of accuracy.

Following the scanning session, participants received a surprise yes/no recognition test. The recognition task consisted of 320 words presented individually. Half were studied during the scanning session (OLD items) and half were unstudied (NEW items). The words remained on the screen until the participant responded as to whether they thought the word was OLD or NEW. If the participant responded OLD, a second phase of the trial was presented, during which time participants were asked to identify the task they had performed with the word at study (MAN-NAT or LRG-SML). All responses were made via a button-press response, and were self-paced. A 500-ms ITI separated each of the recognition trials. The self-paced nature of the recognition task was designed to emphasize accuracy over speed.

Functional Imaging. Images were acquired on a Siemens 1.5 Tesla Vision System (Erlangen, Germany) with a standard circularly-polarized head coil. A pillow and tape were used to minimize head movement. Headphones dampened scanner noise and enabled communication with participants. Both structural and functional images were acquired at each scan. High-resolution (1.25 x 1 x 1) structural images were acquired using a sagittal MP-RAGE 3D T1-weighted sequence (TR=9.7 mm, TE=4, flip=12°, TI=300 ms) (Mugler and Brookeman, 1990) Functional images were acquired using an asymmetric spin-echo echo-planar sequence (TR=2500, TE=50 ms, flip = 90°). Each image consisted of 16 contiguous, 8-mm thick axial

slices acquired parallel to the anterior-posterior commissure plane (3.75x3.75 mm in-plane), allowing complete brain coverage at a high signal-to-noise ratio. Each run consisted of alternating cycles of fixation (A) and task (B) blocks in an ABABA design. The inclusion of fixation blocks was a feature of the scanning design to enable analyses on both tonic and transient effects (Donaldson et al., 2001). Task blocks were approximately 137.5 s long, and they included 20 trials in addition to short periods of fixation that permitted the event-related analyses. Fixation blocks (denoted by a centrally presented crosshair) were 37.5 s in duration. Finally, the first four images in each scanning run were used to allow the scanner to stabilize, and hence were discarded. Each run lasted approximately 6.5 minutes, and a 2-minute delay occurred between runs, during which time participants rested.

Visual stimuli were presented using PsyScope software (Cohen et al., 1993) running on an Apple PowerMac G4. Stimuli were projected to participants with an AmPro LCD projector (model 150) onto a screen positioned at the head end of the bore. Participants viewed the screen through a mirror attached to the head coil. A fiber-optic, light-sensitive key press interfaced with the PsyScope Button Box was used to record participants' behavioral performance.

Data Analysis. Behavioral performance data were analyzed for switching costs by conducting t-tests on accuracy and response time. Successful encoding of stimuli was investigated by measuring recognition accuracy. Recognition accuracy (specifically hit rate) was submitted to a t-test with task-switching condition at encoding as the grouping variable. Because there was a single recognition test after all scanning was completed, the false alarm rate was identical for both the single-task and task-switching conditions, thus obviating the need for a correction. The accuracy of the prior context judgments was analyzed in the same fashion as the hit rates.

Functional imaging data were pre-processed prior to statistical analysis according to the following procedures: 1) functional slices were temporally aligned using sinc-interpolation to account for timing differences during acquisition; 2) corrected for movement using a rigid-body rotation and translation correction (Friston et al., 1996; Snyder, 1996); 3) scaled to achieve a whole-brain mode value of 1000 for each scanning run (to reduce the effect of scanner drift or instability); 4) registered to the participants' structural image following transformation of the structural image into standardized atlas space (Talairach and Tournoux, 1988), using a 12-dimensional affine transformation (Woods et al., 1992; Woods et al., 1998); 5) spatially interpolated to create 3-mm isotropic voxels; 6) spatially smoothed with a 9-mm FWHM Gaussian kernel.

A general-linear model approach (Friston et al., 1995) was used to estimate parameter values for both sustained and event-related responses. Event-related effects were analyzed by estimating values for the various time points within the hemodynamic response epoch. The duration of this epoch was taken to be 20 s (8 scanning frames). The event-related estimates for the time-course data were then submitted to a group analysis using voxel-wise repeated-measures ANOVAs. Event-related responses can be determined in this approach by using time (i.e., scan) as a factor of interest, and examining significant effects of this factor (both main effects and interactions). The primary advantage of this approach is that it makes no a priori assumptions about the particular shape of the hemodynamic response (Buckner and Braver, 1999). Given that the hemodynamic response may vary across brain regions, incorrect estimates regarding its shape may lead to a significant loss of power in detecting event-related effects. State-related effects were estimated by including regressors modeling the difference between blocks of task and blocks of fixation. Although state effects were modeled, they were not found to contribute

substantially to the encoding effects of interest (cf. Otten et al., 2002). Consequently, these effects are not reported further (although see Braver et al., in press).

The statistical analysis procedure was designed to identify brain regions whose event-related activity showed both an effect of the task-switching manipulation as well as a relationship to subsequent memory. To achieve this goal, a conjunction analysis procedure was employed (Price and Friston, 1997), which involved the application of multiple tests, each of which were set at a relatively low threshold. We have used such procedures in previous studies (Braver et al., 2001a; Braver et al., 2001b; Braver and Bongiolatti, 2002) and believe that they optimize the trade-off between power and false-positive protection (i.e., Type II vs. Type I error). In order for a brain region to be accepted as sensitive to both contrasts of interest, all voxels within the region were required to be statistically significant in all tests (described below). The analysis was set up such that any voxel meeting criteria in all statistical tests would have alpha-protection equivalent to $p < .0001$. Moreover, a region was considered significant only if it contained a cluster of 8 or more contiguous voxels. The additional cluster-size requirement ensured an overall image-wise false-positive rate of $p < .05$ (Forman et al., 1995; McAvoy, Ollinger, & Buckner, 2001).

The specific tests conducted were as follows. In order to identify regions that were responsive to both types of contrasts (e.g. subsequent memory and task-switching effects), every voxel in the region had to satisfy the following set of criteria. The estimated time course had to display: 1) an event-related response during single-task trials that were later recognized trials, reflected in a main effect of time in that condition; 2) a positive deflection in the estimated time course during the single-task trials that were later remembered, reflected in a positive correlation with a standard gamma function; 3) an effect of the block manipulation (single-task vs. task-switching) on event-related activity, reflected in a task-switching x time interaction, and either

4a) an overall effect of subsequent memory (later recognized vs. later forgotten), reflected in a subsequent memory x time interaction; or 4b) an interaction between task-switching and subsequent memory, reflected in a task-switching x subsequent memory x time interaction. The first contrast ensures that identified regions are task-related, in that each region is responsive relative to baseline. The second contrast ensures that the analysis included only regions demonstrating positive changes in activation levels. Correlation with a gamma function was used because it takes into account the entire estimated time-course, and does not depend solely on arbitrarily selected time-points. These first contrasts were included to increase the interpretability of the resulting regions; the final tests selected regions that showed sensitivity to the two contrasts of interest.

An additional constraint on the analysis procedure was that only trials that were correctly classified during the semantic task contributed to the estimated time-courses. Further, words were only scored as correctly recognized if during the recognition test, the participant both accurately identified the word as OLD and correctly recollected the task that was performed when it was seen originally (item hit, source hit: see Davachi et al., 2003). Trials in which the participant correctly identified a word as OLD but incorrectly identified the prior context were treated as a separate condition (item hit, source miss). These trials were not analyzed, because successful recognition of the word was highly correlated with successful recollection of the study task, thus resulting in very few source failure trials. Recognized trials were contrasted with miss trials, on which participants mistakenly classified an old item as "NEW." As such, subsequently recognized trials entailed both item recognition and source recollection (and hence might correspond to items remembered with high confidence), whereas forgotten trials entailed a failure in item recognition.

Regions-of-interest (ROIs) identified through these conjunction procedures were then subjected to one further analysis; this analysis validated that all effects tested in the voxel-wise conjunction analysis were statistically significant ($p < .05$) at the ROI level. This final test was added to ensure that each region showed a similar response across the voxels within it. It is conceivable that each of the voxels could pass each of the tests mentioned above, but in different directions; if this were the case, then the effects would cancel out in the ROI level analysis, and not meet this final criterion. All regions described below passed this test. For ROI analyses (and Figures 2-4), data are expressed in terms of mean percent signal change relative to the fixation trials within a task block.

RESULTS

Behavioral data

Overall, behavioral performance was high in the semantic judgment tasks, with participants averaging 94% accuracy across the two conditions (see Table 1). Under the task-switching condition, participants were slower ($t(12)=5.36$, $p < 0.001$) and less accurate ($t(12)=3.85$, $p < 0.01$) than in the single-task condition, revealing a behavioral cost for item-level processing due to the additional task-level computations required during the task-switching condition.

Later recognition performance was generally high (HIT=64.3%, FA=5.1%), indicating that participants were often successful at encoding the studied items and the context in which the items were processed. However, there was a significant effect of task-switching on successful recognition. Significantly more words were recognized from the single-task condition than from the task-switching condition ($t(12)=5.61$, $p<.001$; Table 1). Participants were highly accurate at source recollection given that they recognized the word as OLD (Mean Source Recollection

Accuracy = 83.7 %), and there was no effect of task-switching on these source recollection judgments ($p > 0.9$). However, this latter finding must be treated with caution as it differed from that obtained in a larger sample behavioral pilot study. In the pilot study, source recollection was significantly poorer for words encoded in the task-switching block.

Neuroimaging data

Six brain regions met the criteria for showing effects of the task-switching manipulation as well as a relationship to subsequent memory (Table 2, Figure 1). These regions were primarily located in the left hemisphere, and included LIPC, bilateral superior parietal cortex, and medial parietal cortex / precuneus. Of particular interest were the regions found in LIPC and precuneus.

Left inferior prefrontal cortex. An extended region in LIPC was sensitive to both the blocked manipulation of task-switching ($F(7,84)=4.34$, $p < 0.001$) and the analysis contrasting subsequently remembered and subsequently forgotten words ($F(7,84)=4.73$, $p< 0.001$; see Figure 2A). Critically, these effects indicated that LIPC showed (a) a standard increase in activity associated with subsequently remembered words relative to subsequently forgotten words, and (b) a novel pattern wherein activity was greater in the condition resulting in, on average, worse overall subsequent memory performance (i.e., task-switching > single-task). These two effects — subsequent memory and task switching — did not interact ($F < 1$). Thus, LIPC activity tracked both item-level fluctuations in semantic processing that were positively associated with encoding processes (as indexed by subsequent memory outcome), and task-level processes involved in the retrieval, instantiation, and maintenance of the relevant semantic context, which were negatively correlated with encoding. The latter negative correlation presumably reflects the fact that these task-level computations diverted LIPC resources away from item-level encoding processes.

Additional analyses were performed to further decompose activation within the task-switching block. If the semantic operations associated with task-switching diverted resources away from item-level encoding processes, then this negative encoding effect might be strongest under conditions where task-switching demands were most acute (e.g. on the trials in which the task switched compared to the trials in which the task-repeated). The task design was such that within task-switching blocks, only 50% of the trials were actual task-switch trials, while the other 50% were task-repeat. Behavioral performance indicated that task-switch trials were encoded less effectively than task-repeat trials ($t(12)=1.92$, $p < 0.05$, one-tailed). Surprisingly, including this distinction in an additional analysis indicated that the event-related response in this region of LIPC displayed no differential pattern of response to task-switch and task-repeat trials ($F(7,84) = 1.35$, $p > 0.2$; see Figure 2B). Task-switch status did not interact with subsequent memory ($F < 1$). This outcome suggests that during the task-switching block, LIPC mechanisms were diverted to the task-level on both task-switch and task-repeat trials. The implication of this finding for understanding LIPC function and subsequent memory effects is considered in the Discussion.

Medial Parietal Cortex / Precuneus. Medial parietal cortex / precuneus was also sensitive to the contrasts of task-switching and subsequent memory (Figure 3A). This region displayed a greater response in the task-switching condition relative to the single-task condition ($F(7,84)= 4.34$ $p < 0.001$), but the region did not display a direct effect of subsequent memory ($F(7,84)= 1.12$ $p > 0.3$). Rather, subsequent memory status interacted with the task-switching manipulation ($F(7,84)=3.21$, $p < 0.005$), indicating that there was a different event-related response during the processing of subsequently forgotten words relative to subsequently remembered words, but this was statistically significant only in the task-switching condition (task-switching: $F(7,84)=3.23$, $p < 0.005$; single task: $F(7,84)=1.13$, $p > 0.3$).

Decomposing the task-switching block into switch and repeat trials produced results similar to that in LIPC. Again, task-switch and task-repeat trials were not significantly different ($F < 1$; see Figure 3B). However, the distinction further illuminated the task-switching x subsequent memory x time interaction found in the prior analysis, indicating that the subsequent memory x time interaction was significant only for task-switch trials ($F(7,84) = 3.10$, $p < 0.01$; task-repeat: $p > 0.4$).

DISCUSSION

A network of 6 brain regions was found to be sensitive to both the task-switching manipulation and the subsequent memory analysis. In particular, LIPC was more active during the processing of items in the task-switching block relative to items in the single-task block, and during the processing of subsequently remembered relative to subsequently forgotten items. Additionally, a region in medial parietal cortex / precuneus also displayed sensitivity to both contrasts. This region elicited greater responses to items in the task-switching block relative to items in the single-task block and an interaction between task-switching status and subsequent memory, such that there were different event-related responses to subsequently remembered and forgotten words only during the task-switching block.

Processes associated with LIPC

The present study revealed new evidence regarding the relation between LIPC activation and episodic encoding: LIPC activation was greater under task conditions that produced, on average, lower subsequent memory performance and presumably less effective encoding. That is, LIPC activation was greater in the task-switching relative to the single-task condition, although items encountered in the task-switching condition were not remembered as well as those encountered in the single-task condition. This result indicates that the general positive

relationship between LIPC activity and encoding processes does not always hold. As such, the results rule out a naïve model in which the magnitude of activity in LIPC during semantic processing is thought to always reflect processes that impact something analogous to the "strength of encoding." Consequently, one can infer that even though subsequent recognition may be reliably associated with greater LIPC activity, the reverse relationship does not hold. It is not the case that task manipulations that increase activity in LIPC will necessarily lead to more effective encoding, and in fact, such manipulations may actually reduce encoding success, as observed here. As such, this pattern should serve as a constraint on any functional interpretations of the cognitive operations subserved by LIPC and their relation to episodic encoding.

Concurrently, the presently reported subsequent memory effect in LIPC also replicates previous findings showing that this region demonstrates greater event-related responses during the encoding of subsequently remembered relative to subsequently forgotten words (Baker et al., 2001; Brewer et al., 1998; Henson et al., 1999; Kirchhoff et al., 2000; Otten et al., 2001; Wagner et al., 1998). As the recognition memory task classified words as remembered on the basis of both the participant recognizing the word as having been previously encountered and recollecting the semantic context in which the word was studied, these finding provide further evidence that LIPC encoding activation is positively correlated with subsequent memory, when accompanied by recollection (Davachi et al., 2003). The findings are consistent with the hypothesis that trial-by-trial fluctuations in item-level LIPC processes are related to subsequent memory and presumably impact encoding efficacy under conditions in which the encoding task is held constant.

One account of the present data is that left frontal responses reflect two separable component processes that subserve controlled semantic retrieval: (a) retrieval, instantiation, and maintenance of the current conceptual context/goal, when required (e.g. Bunge et al., in press),

and (b) the use of this context/goal representation to retrieve task-relevant semantic knowledge about items (Fletcher et al., 2000; Wagner et al., 2001). Modulations in the latter process appear to be correlated with later retrieval outcome, and thus encoding efficacy, whereas modulations of the former process need not correlate with retrieval outcome. As presently observed, when modulations of the former process divert resources away from the latter, these modulations can even be negatively correlated with subsequent memory performance. The differences in activity between single-task and task-switching items reflect an increase in the amount of task-level processes required to manage the constantly changing context in the latter condition, and as such mark the diversion of resources away from item-level processes that typically positively impact encoding. This finding is similar to that reported by Otten, Henson, & Rugg (2002), who found that state-related activity in LIPC was negatively correlated with subsequent memory performance. They argued that state- and item-related mechanisms may trade-off, such that the discriminability of the event-related response is greatest when state-level activity is low. The current data support and extend these previous results by finding a negative correlation between subsequent memory performance and the event-related response of LIPC, where the experimental manipulation yielding this negative association is thought to index task-level influences on the event-related signal.

Further insight into the nature of the task-level LIPC processes that are negatively associated with subsequent memory can be garnered from the comparison between task-switch and task-repeat trials. This contrast revealed that, although there were no differences in the event-related responses to these two conditions, both conditions elicited greater event-related responses compared to single-task trials. This pattern indicates that the increased activity associated with the task-level processing is not solely due to the instantiation of a “new” task-representation,

which might occur only on task-switch trials. Rather, this finding suggests that participants were actively maintaining both task representations in accessible states across trials within the task-switching block, and then favoring the currently appropriate one. Accordingly, increased LIPC activity levels in the task-switching block relative to the single-task block may reflect increased maintenance demands and/or greater reliance on mechanisms required to resolve competition between the alternative task-goals. As such, when LIPC bias mechanisms are diverted to support semantic context maintenance or the resolution of competition between competing contexts, this diversion of LIPC mechanisms away from item-level processing results in a negative consequence for item encoding.

This negative correlate of encoding within LIPC clearly indicates that the event-related response of this region does not always support encoding. It is possible that this finding could be generalized, such that under some circumstances, even item-level processing is not always positively correlated with retrieval outcome. Although the current data do not speak to such effects, there have been demonstrations in the cognitive psychology literature of deep semantic encoding processes leading to poorer recognition performance when the retrieval cues are mismatched to the encoding context (e.g. Morris et al., 1977; Tulving, 1983). Under these conditions of "encoding-retrieval interactions," one might expect to see a negative relation between activity during encoding and subsequent memory for non-semantic features of a prior experience. That is, item-level subsequent memory effects likely do not reflect differences in some global measure of encoding efficacy, but likely reveal differences in the encoding of particular kinds of event features (semantic, phonological, visuo-perceptual, etc: Paller and Wagner, 2002).

Relationship to previous findings in LIPC.

Previous studies investigating the role of LIPC have found that different regions of LIPC tend to be separable along an anterior/posterior distinction (Buckner et al., 1995; Fiez, 1997; Poldrack et al., 1999). Anterior regions of LIPC (aLIPC) appear to be more involved in the controlled retrieval of semantic information, whereas posterior regions of LIPC (pLIPC) appear to be more involved in the processing of phonological / lexical-semantic properties of words and objects (e.g. Gabrieli et al., 1998). The conditions that elicit activation in these two regions are highly overlapping, and thus one can only functionally dissociate them with tightly controlled experiments (Poldrack et al., 1999; Roskies et al., 2001). The present experiment was not designed to tease apart these two LIPC subregions, and as such, the large region of LIPC activation presently observed includes both subdivisions.

With respect to this prior literature on LIPC function, the present findings parallel those from a recent study of LIPC activation during phonological processing of words and pseudo-words. Clark and Wagner (2003) scanned participants while they performed syllable judgments on either pseudo-words (e.g., HAMDER) or English words (e.g., HAMPER), and then analyzed the encoding data as a function of subsequent recognition performance. Their results revealed that pLIPC activity in the syllable-judgment task was greater when processing pseudo-words than when processing English words, even though overall memory for pseudo-words was worse than that for English words. Additionally, they found that the difference in encoding activation between subsequently remembered and forgotten items was greater for pseudo-words than for English words. They suggested that this interaction reflected the fact that pLIPC supported the encoding of the pseudo-word and word trials, and further, that the phonological control processes supported by pLIPC were *more* important in the pseudo-word condition because no lexical representation was present in long-term memory to facilitate the orthographic-to-phonological

mapping required at encoding. Moreover, in contrast to known words, pseudo-words lack associated semantics, thus making phonological representations particularly salient at the time of retrieval, and thus particularly important at the time of encoding. As such, the increase in pLIPC activity associated with the processing of pseudo-words was hypothesized to support phonological encoding processes.

In contrast to the findings and hypothesis of Clark and Wagner (2003), the current data suggest that the increased LIPC activity between the mixed- and single-task blocks mark processes that are detrimental to item encoding. Additional inspection of the timecourses in the task-switching block provide further support for this argument, and suggest that the trend in the current study is the opposite than that found in Clark and Wagner (2003), such that the difference between subsequently remembered and subsequently forgotten words is numerically smaller in the condition that leads to greater average activity (task-switching blocks) compared to the condition leading to lower average activity (single-task blocks), particularly in the 5th frame. Formally, the subsequent memory x time interaction was only significant for the trials within the single-task block ($F(7,84) = 3,58$ $p < 0.005$), and it was not significant for the trials within the task-switching block ($F(7,84) = 1.56$, $p > 0.15$), indicating that there were differential event-related responses to subsequently remembered and subsequently forgotten words in the single-task condition, but not in the task-switching condition. This apparent divergence with the findings of Clark and Wagner likely reflects the fact that LIPC activation in the Clark and Wagner experiment marked the engagement of exclusively item-level mechanisms, whereas LIPC activation in the present study marked both item-level and task-level processes. As discussed above, when LIPC mechanisms are diverted from the item to the task level, it is under such situations the LIPC neural signals may negatively correlate with memory formation.

Negative correlates of encoding and medial parietal / precuneus

Several recent papers have examined at the relationship between brain activity during encoding and later forgetting, e.g. negative correlates of encoding (Davachi et al., 2001; Otten and Rugg, 2001; Wagner and Davachi, 2001). In a task-switching encoding condition, Otten & Rugg (2001) found several regions that showed greater event-related responses to subsequently forgotten compared to subsequently remembered words. One region that they observed to show this pattern — medial parietal cortex — is analogous to the medial parietal / precuneus region identified in the present study. Although similar regions have been reported in the context of other event-related designs (e.g. Wagner and Davachi, 2001), it is less clear whether blocked manipulations of encoding result in such effects, as previous blocked manipulations of encoding have focused on positive correlates of later remembering.

Importantly, the medial parietal cortex / precuneus region identified in the present experiment was sensitive to *both* the blocked manipulation and item-by-item fluctuations in encoding. This region showed a greater hemodynamic response during trials in the task-switching condition relative to trials in the single-task condition, and further showed an interaction between this blocked manipulation and trial-by-trial fluctuations, such that subsequently remembered and forgotten words had different timecourses only under the task-switching conditions. Moreover, the effects of task-switching were only observed on the task-switch trials within the block. Previous studies have suggested that regions in medial parietal cortex are involved in the selection of response-relevant information (Rowe et al., 2000). The current experimental manipulation of task-switching (and also the encoding conditions of Otten & Rugg, 2001) should have a particularly strong impact on this process because the relevant task-dimension (and the associated stimulus-response mapping) changes dynamically on a trial-by-trial basis. Thus, there

should be a higher demand placed on response selection processes, specifically on the task-switch trials that produce a change in the relevant stimulus-response mapping rules. The increased response selections demands reflected in medial parietal activity might also provide a measure of the extent to which processing resources are diverted away from the required elaborative encoding required to create a robust memory trace.

Relationship to the previous studies of divided attention and encoding

One perspective of the current task manipulation is that the task-switching condition reflects encoding under divided-attention, whereas the single-task condition reflects encoding under full-attention. The task-switching condition could be considered a divided-attention condition because attentional resources have to be shared among processes that enable the updating of task-sets and processes that enable appropriate semantic classification. Previous neuroimaging studies of divided attention have found decreases in activity in LIPC associated with divided-attention conditions relative to full-attention conditions (Anderson et al., 2000; Iidaka et al., 2000; Kensinger et al., 2003; Shallice et al., 1994). However, a task analysis of these previous neuroimaging studies of divided attention and encoding reveal critical differences between these earlier manipulations of divided attention and the present manipulation. Specifically, previous studies have used secondary tasks that were not semantic in nature; the secondary tasks were either motor (Shallice et al., 1994) or auditory discrimination tasks (Anderson et al., 2000; Iidaka et al., 2000; Kensinger et al., 2003). There is no reason to think that non-semantic secondary tasks serve to increase activity in LIPC. Further, if less semantic processing were occurring on each trial (as is possibly the case under such divided attention conditions), then one would predict that the hemodynamic responses in those conditions should in fact be reduced. This is indeed what these earlier studies observed.

Importantly, in contrast to a non-semantic diversion of attention, the current manipulation of attentional load directly involved semantic processing, and as such, may have caused its effects via direct interference. Thus, whereas previous studies found greater LIPC activity in full- relative to divided-attention conditions because their secondary tasks reduced the amount of general processing resources devoted to item-based semantic encoding, the current study found an increase in LIPC activity during the 'divided-attention' condition due to an increased demand on semantic processing. Critically, these increased demands at the task level resulted in interference at the item level. In this manner, the present study provides novel evidence indicating that LIPC activity reflects at least two separable components: 1) the retrieval, instantiation, and maintenance of appropriate semantic context representations, and 2) the use of this semantic context knowledge to bias semantic space. The latter process is typically positively correlated with subsequent memory performance, but the former is not.

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Table 1

Behavioral Performance

□	SINGLE-TASK	TASK-SWITCHING
Response Time (ms)	968.8 (54.03)	1091.1 (85.2)
Accuracy	95.5 (1.3)	93.0 (1.1)
Percent Remembered	70.2 (8.3)	58.6 (9.8)
Context Judgment Accuracy	83.8 (3.7)	83.7 (3.6)

Data refer to group means with 95 % confidence intervals in parentheses.

Table 2

Regions of Interest

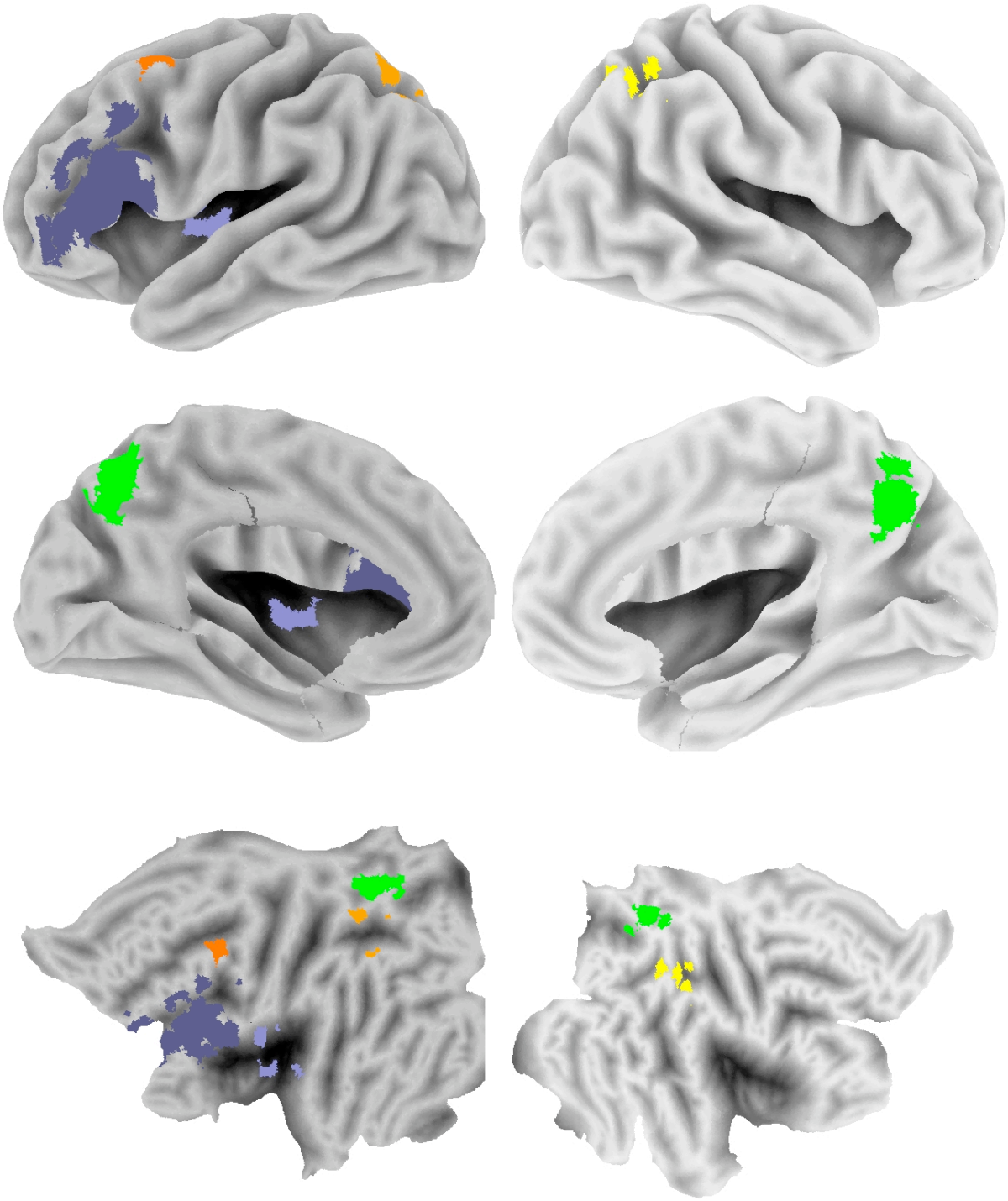
Brain Region	Brodmann area	X	Y	Z	Size (mm^3)
Left inferior prefrontal cortex	44/45	-46	21	15	7047
Left posterior insula	NA	-44	-15	9	243
Left superior parietal	7	-32	-72	48	324
Medial parietal cortex / precuneus	7	-2	-66	42	1998
Right superior parietal	40/7	34	-60	45	378
Left supplementary motor	6	-32	6	54	243

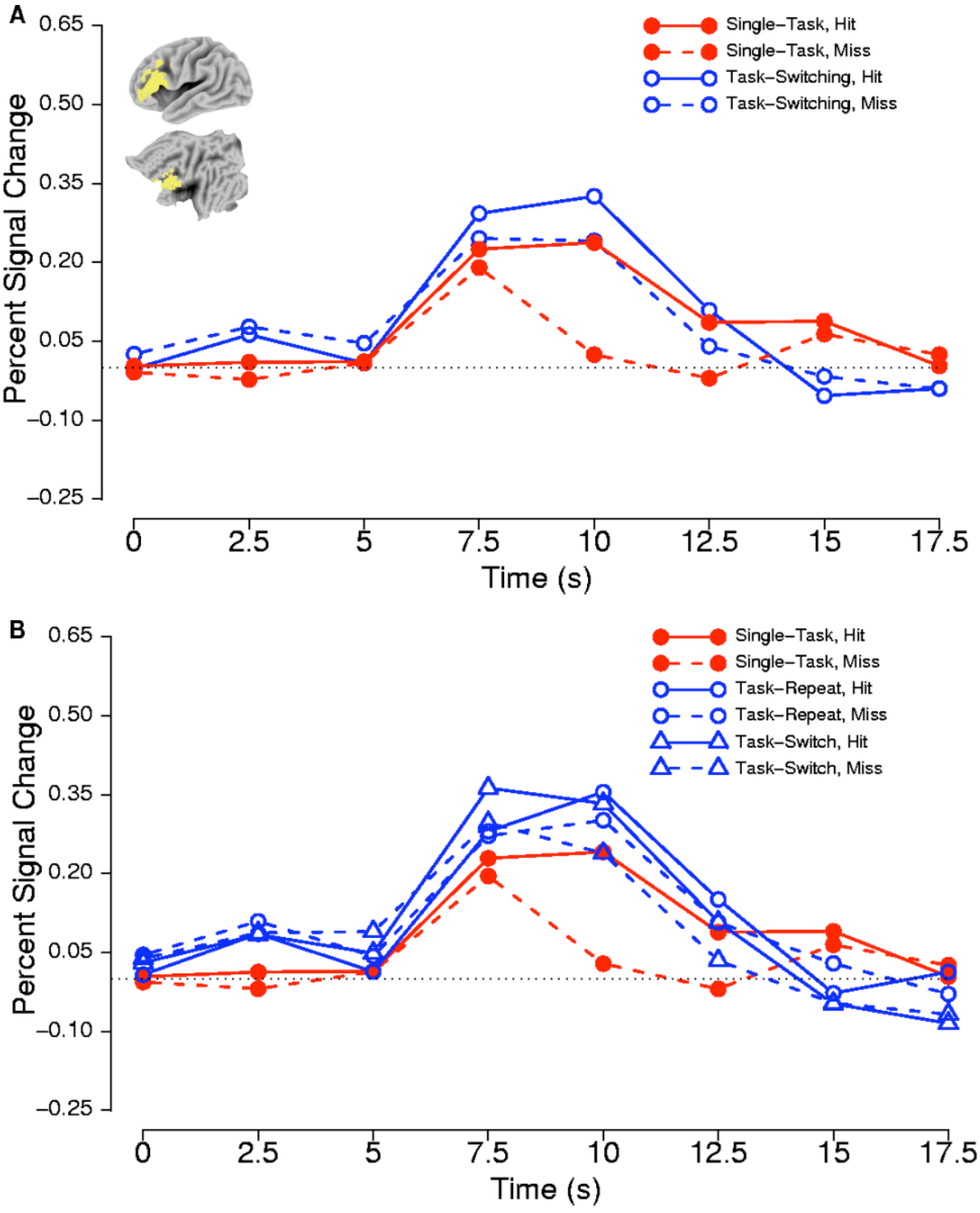
Figure Captions

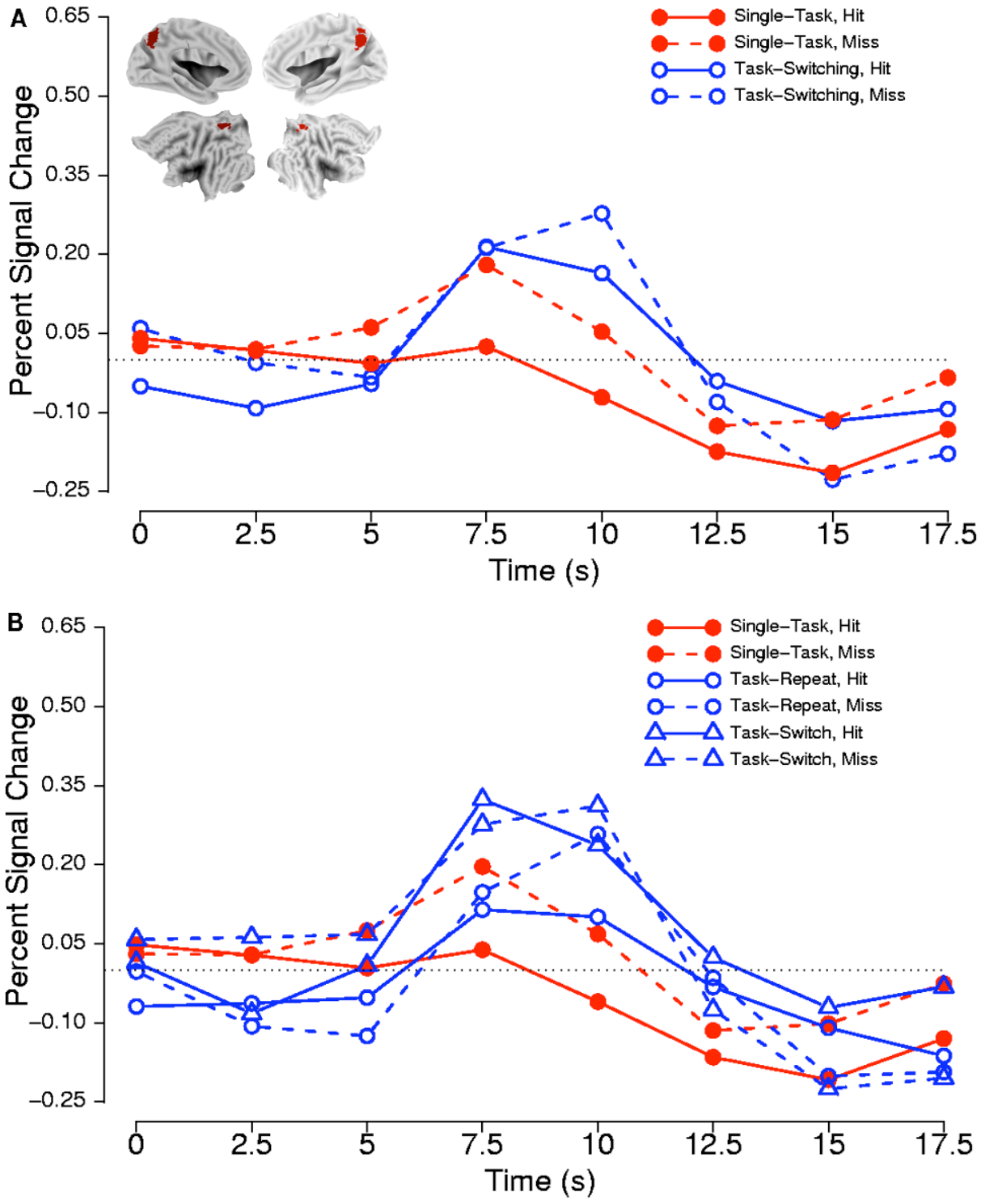
Figure 1. All identified brain regions, projected onto lateral and medial views of inflated cortical surfaces and flat maps. Color identifies different regions. These projections were created using CARET software (Van Essen et al., 2001)

Figure 2. Region identified in left inferior prefrontal cortex (center of mass: -46, 21, 15), and its corresponding time courses. (A) Estimated time courses associated with the remembered (hit) and forgotten (miss) items in each of the two types of blocks. (B) Estimated time courses: trials from the task-switching block have been additionally decomposed in to task-repeat trials in which the task was the same as that on the previous trial, and task-switch trials, in which the task was different on the previous trials.

Figure 3. Region identified in medial parietal cortex / precuneus (center of mass: -2, -66, 42), and its corresponding time courses. (A) Estimated time courses associated with the remembered (hit) and forgotten (miss) items in each of the two types of blocks. (B) Estimated time courses: trials from the task-switching block have been additionally decomposed in to task-repeat trials in which the task was the same as that on the previous trial, and task-switch trials, in which the task was different on the previous trials.




A
Single–Task, Hit
Single–Task, Miss
Task–Switching, Hit
Task–Switching, Miss
Percent Signal Change
0.65
0.50
0.35
0.20
0.05
–0.10
–0.25
0
2.5
5
7.5
10
12.5
15
17.5
Time (s)
B
Single–Task, Hit
Single–Task, Miss
Task–Repeat, Hit
Task–Repeat, Miss
Task–Switch, Hit
Task–Switch, Miss
Percent Signal Change
0.65
0.50
0.35
0.20
0.05
–0.10
–0.25
0
2.5
5
7.5
10
12.5
15
17.5
Time (s)


A
Single–Task, Hit
Single–Task, Miss
Task–Switching, Hit
Task–Switching, Miss
Percent Signal Change
0.65
0.50
0.35
0.20
0.05
–0.10
–0.25
0
2.5
5
7.5
10
12.5
15
17.5
Time (s)
B
Single–Task, Hit
Single–Task, Miss
Task–Repeat, Hit
Task–Repeat, Miss
Task–Switch, Hit
Task–Switch, Miss
Percent Signal Change
0.65
0.50
0.35
0.20
0.05
–0.10
–0.25
0
2.5
5
7.5
10
12.5
15
17.5
Time (s)