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Spatio-Temporal Dynamics of Neural Mechanisms Underlying Component Operations in Working Memory

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Abstract

Neuroimaging and neurophysiology evidence suggests that component operations in working memory (WM) emerge from the coordinated interaction of posterior perceptual cortices with heteromodal regions in the prefrontal and parietal cortices. Still, little is known about bottom-up and top-down signaling during the formation and retrieval of WM representations. In the current set of experiments, we combine complementary fMRI and EEG measures to obtain high-resolution spatial and temporal measures of neural activity during WM encoding and retrieval processes. Across both experiments, participants performed a face delayed-recognition WM task in which the nature of sensory input across stages was held constant. In experiment 1, we utilized a latency-resolved fMRI approach to assess temporal parameters of the BOLD response during stage-specific encoding and retrieval waveforms. Relative to the latency at encoding, the PFC exhibited an earlier peak of fMRI activity at retrieval showing stage-specific differences in the temporal dynamics of PFC engagement across WM operations. In experiment 2, we analyzed the first 200ms of the ERP response during this WM task providing a more sensitive temporal measure of these differences. Divergence of the ERP pattern during encoding and retrieval began as early as 60ms post-stimulus. The parallel fMRI and ERP results during memory-guided decisions support a key role of the PFC in top-down biasing of perceptual processing and reveals rapid differences across WM component operations in the presence of identical bottom-up sensory input.

1. Introduction

In recent years, significant advances have been made in understanding the function of the prefrontal cortex (PFC). It is proposed that goal-directed behavior depends critically on the PFC. The extensive reciprocal connections between the PFC and multiple cortical and

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subcortical structures place the PFC in a unique neuroanatomical position to monitor and manipulate diverse cognitive processes.

The results of experiments in behaving monkeys using recordings from single units in the lateral PFC have consistently found persistent, sustained levels of neuronal firing during the retention interval in tasks which require a monkey to retain information for a brief time (e.g. seconds) (Funahashi et al., 1989; Fuster and Alexander, 1971; Kubota and Niki, 1971). This sustained activity is thought to provide a bridge between the stimulus cue, which could be, for instance, the location of a flash of light, and its contingent response, which could be in this example a saccade to the remembered location. These results have been supported by functional imaging studies in humans and there is now a critical mass of studies of neural activity in the lateral PFC in humans during delay tasks (for review, see Curtis and D'Esposito, 2003). Thus, the existence of persistent neural activity during blank memory intervals of delay tasks is a powerful empirical finding that lends strong support for the hypothesis that the lateral PFC is a critical node supporting active maintenance of task-relevant representations. The necessity of this region for active maintenance of task-relevant representations has also been demonstrated by studies that have found impaired performance on delay tasks in monkeys with selective lesions of the lateral PFC (Bauer and Fuster, 1976; Funahashi et al., 1993).

These physiological and lesion studies provided evidence suggesting that the primary function of the lateral PFC is to create and maintain internal representations of relevant sensory information necessary for guiding behavior. Miller and Cohen (2001) extended this hypothesis by suggesting that in addition to recent sensory information, integrated representations of task contingencies and even abstract rules (e.g., if this stimulus then this later response) are also maintained in the PFC. This is similar to what Fuster has long emphasized (Fuster, 1997) - namely, that the PFC is critically responsible for temporal integration and the mediation of events that are separated in time but contingent on one another. Thus, sustained delay-period activity likely reflects not only the maintenance of many goal-directed representations such as past sensory events (i.e., a retrospective code), but also representations of anticipated action and preparatory set (i.e., prospective codes) (D'Esposito et al., 2000; Quintana and Fuster, 1993). In this way, the PFC - by the nature of the information it represents - can provide direct top-down feedback signals to posterior association cortex that is processing incoming sensory input from a particular modality (e.g. visual or auditory).

Although the role of the PFC in top-down signaling is based more on suggestive findings than on direct empirical evidence (Miller & D'Esposito, 2005), a few studies do lend direct support to this hypothesis. For example, Fuster and colleagues (Fuster et al., 1985) investigated the effect of inactivation of specific parts of the PFC by cooling on spiking activity in inferotemporal cortex (ITC) neurons during a delayed-match-tosample color task. Inactivation of the PFC during the delay interval of this task, when persistent stimulus-specific activity in ITC neurons is normally observed, caused attenuated spiking profiles and a loss of stimulus-specificity of ITC neurons. These two alterations of ITC signaling strongly implicate the PFC as a source of top-down signals necessary for maintaining robust sensory representations in the absence of bottom-up sensory activity. In humans, combined

lesion and EEG studies also support a key role of PFC control of posterior cortices in attention tasks with PFC-extrastriate top-down control evident in the initial 100–150 milliseconds of processing of an attended visual event (Barcelo et al., 2000; Yago et al., 2004).

One aim of the present study was to further explore the role of the PFC in top-down modulation by investigating latency measures as a potential source of evidence for these interactions. Information regarding the timing of events across cortical regions provides insight into neural interactions during goal-directed behavior. Comparisons across regions can provide information about the directionality of signal propagation between two areas interacting within a distributed network. For example, if the onset of activity in area A precedes the activity of area B, this relative ordering can index feedforward or feedback interactions between cortical regions. In human studies, convergent evidence from combining functional MRI (fMRI) and event-related potentials (ERP) could provide such data but has been an underutilized approach. In this study, our goal was to study the relationship between timing of events in multimodal cortical regions in the PFC, and posterior unimodal cortical regions that these regions may be interacting with. We utilized a classic delayed recognition task with faces as stimuli, which allowed us to localize a region of interest within ITC. Moreover, this task allowed us to examine inter-regional relationships at different stages of the task. Thus, we were able to investigate the timing of events when task-relevant representations are encoded, as well as during the retrieval stage, when decision processes require utilization of task-relevant representations that are being actively maintained.

Druzgal & D'Esposito, (2003) examined the differential contribution of the PFC and the fusiform face area (FFA) during visual working memory (WM). In a post-hoc analysis of temporal patterns across regions, they reported an earlier time-to-peak of the fMRI response in the FFA compared to the PFC during the encoding stage of the task. This pattern is consistent with a model in which visual signals are first relayed in a bottom-up manner from sensory association cortex to higher order areas that may then guide strategic mnemonic encoding processes. Consistent with this possibility, the magnitude of PFC activity during WM encoding has been shown to track with the number of to-be-remembered items (Rypma et al., 1999; Jha & McCarthy, 2000) and also predicts successful performance following WM delays (Pessoa et al., 2002; Rypma & D'Esposito, 2003). Corresponding increases in posterior visual processing of to-be-remembered stimuli versus to-be-ignored stimuli during encoding (Gazzaley et al., 2005) suggests that following the processing of visual information and identification of task-relevant stimuli, the PFC may then guide stimulus processing in a top-down manner.

Interestingly, during the retrieval stage of the Druzgal & D'Esposito (2003) experiment – during which the participants made match/non-match decisions in response to a probe face – there was a reversal in this temporal relationship, with the PFC showing an earlier peak than the FFA. This reversal in relative timing across stages suggests that memory-guided decision making may involve an early top-down signal to posterior regions to initiate and control retrieval processes. Evidence derived from a meta-analysis of spiking patterns during memory-guided visual search suggests that PFC neurons (Rainer et al., 1998) display target-

sensitive firing at 140ms while similar firing in ITC neurons (Chelazzi et al., 1993) lags behind at 180ms. Thus, while encoding might proceed in a bottom-up manner in which stimuli are first processed in posterior visual regions and then assigned behavioral relevance by the PFC, the PFC might be engaged early at retrieval to trigger top-down signals necessary for comparing a stored internal representation with a current visual stimulus to guide a response (Schall, 2001). A series of recent studies in cats and monkeys employing multi-site recordings of single-unit and local field potential signals also emphasize the role of network interactions and top-down control in cognitive processing (Buschman & Miller, 2007; Womelsdorf et al., 2007; Saalmann et al., 2007).

Due to its simultaneous whole-brain sampling and recent innovations in experimental design and analysis (Menon et al,. 1998, Formisano & Goebel, 2002), fMRI is emerging as a valuable tool for tracking the temporal involvement of distributed brain areas in cognitive tasks in humans. In experiment 1, we investigated bottom-up and top-down interactions between regions during WM encoding and retrieval operations using a latency-resolved fMRI approach explicitly aimed at measuring stage-specific regional timing measures. While fMRI has made remarkable progress in localizing cognitive processes, it has been much less successful in detecting the temporal characteristics of these processes. Due to the sluggishness of the BOLD response, signals for adjacent events in a complex multi-stage cognitive process such as WM are inherently overlapping in the recorded signal. This renders it difficult to tease apart the components of the overall BOLD response in WM tasks that specifically reflect the neural mechanisms underlying subcomponent WM operations. In this experiment, we employed a design and analysis strategy capable of separately estimating subcomponent stages in a multi-component cognitive event without requiring potentially faulty assumptions about the shape of the HRF (Ollinger et al., 2001a, b). Then, by employing a model-fitting algorithm to these estimated time-courses (Miezin et al., 2000), time-to-onset and time-to-peak parameters were derived for each response during each processing stage. In experiment 2, we performed an ERP experiment which has superb temporal resolution but lacks the spatial resolution of fMRI. Given methodological challenges inherent to latency-resolved fMRI, these electrophysiology measures provide a power complement to hemodynamic latency measures and allow a more complete and resolved comparison of early evoked responses to cue and probe stimuli of a delay task. By comparing these temporal parameters across regions in both fMRI and ERP data, we aim to test the Druzgal & D'Esposito (2003) findings that encoding and retrieval processes rely upon bottom-up and top-down interactions between unimodal and multimodal cortical regions.

2. Results

EXPERIMENT 1

Behavioral performance—Subjects were highly accurate recognizing the cue as matching or non-matching to the probe. The average hit rate was 0.93 (SD = 4.73).

Relative timing measures of FFA and PFC across WM stages—To quantitatively assess the different temporal responses across the encoding and retrieval stages, we

performed a region (FFA vs. LMFG vs. RMFG) by condition (encoding vs. retrieval) ANOVA on time-to-onset and time-to-peak measures of the estimated BOLD stage-specific responses followed by post-hoc statistical comparisons across specific regions.

Using the time-to-peak measures, there was a significant region X condition interaction ($F[1,6] = 6.035$, $p<0.05$) demonstrating temporal differences in the ROIs across stages with identical bottom-up input. Using the time-to-onset measures, this interaction did not reach significance. Thus, time-to-peak measures in the FFA were later at retrieval period than during the encoding period ($p=0.04$; Table 1). On the other hand, the left MFG showed the opposite pattern in that the time-to-peak during retrieval was significantly more rapid than during encoding ($p=0.03$; Table 1). There were no differences in right MFG across task stages.

Planned comparisons showed that at the onset of the cue, the time-to-onset and time-to-peak responses in the left and right MFG ROIs all significantly lagged behind the FFA by an average of at least 1000ms ($p<0.02$; see waveforms in Figure 1, left and a summary of timing values in Table 1). At the onset of the memory probe, there was no statistical difference found in the time-to-onset between the FFA and the left or right MFG. However, the time-to-peak of activity in the left MFG preceded time-to-peak in the FFA ($p<0.05$, figure 1, right).

Collectively, these statistical analyses show both within-region differences in response across task operations as well as different relative timing across regions during WM encoding and retrieval.

EXPERIMENT 2

Behavioral performance—Subjects were accurate recognizing the cue as matching or non-matching to the probe. The average hit rate was 0.92 (SD = 5.36).

General description of ERPs—Figure 2 presents the responses to the cue and probe in match and non-match conditions. The most noticeable differences were seen between the response to the cue and probe. There was a more negative response to the probe at fronto-central electrodes at the early stage (60–220ms), and at occipito-temporal electrodes subsequently (220–350ms). This was replaced by a stronger positivity for probes starting at the vertex at 350ms and spreading along the next 500ms to cover most of the scalp (Figure 3). We concentrate in this report on the early phase, including the initial perceptual part of the response (Figure 4).

Detailed analysis of the initial 220 ms—We first examined the a-priori defined face-related components N170 (Bentin et al., 1996) and the vertex positive potential (VPP; Jeffreys, 1989; Itier & Taylor, 2002, see Joyce & Rossion, 2005, for a recent comparison of these components). These components were indeed the most evident responses in the first 220 ms after stimulus onset and were elicited by face stimuli in all conditions (Figure 4). Congruent with their reported sensitivity to faces, these responses were not elicited by the non-face catch trials (Figure 4). Thus, a normal N170/VPP “face effect” was observed in the present paradigm.

The N170 was maximal as expected at the P9 and P10 electrodes, and the VPP was maximal at Cz. Both peaked at 160–164 ms for all conditions. N170 and VPP amplitude were measured in each subject as the average of 5 data points surrounding the peak latency at the grand average (i.e., 152–172 ms). There was no difference between conditions at P9-10 (N170). A 3-way ANOVA of the N170 with factors Task Period (Cue, Probe), Probe Type (Match, Non-match) and Hemisphere (left: P9, right: P10) found no significant main effects or interactions. A trend was found towards a stronger response on the right, as typical for the N170 elicited by faces ($F(1,14) = 3.85$, $P = 0.07$). A second analysis, in which individual subject N170 peaks were detected and used to determine the latency of the N170, did not reveal any significant latency difference between conditions nor an interaction.

In contrast to the N170, the fronto-central VPP was more positive for the cue than for the probe (Figure 4, top). A 3-way ANOVA with factors Task Period (Cue, Probe), Probe Type (Match, Non-match) and Electrode (Fz, FCz, Cz, and Pz) found a significant main effect of Task Period ($F(1,14) = 20.8$, $p < 0.0005$) as well as a main effect of electrode ($F(3,12) = 10.45$, $p < 0.005$). Post-hoc contrasts showed that the VPP was larger at Cz then in FCz or in Fz. There was no significant main effect of similarity, nor any significant interaction among the factors. Thus, the VPP was significantly reduced during the probe presentation relative to the cue presentation, independent of whether the cue matched the probe. However, inspection of the waveforms (Figure 4 top) revealed that the negative shift of the probe waveforms (match and non-match alike) started in fact much earlier then the VPP latency, suggesting that the change in the VPP amplitude might be the result of summation with an overlapping slower activity.

To determine the earliest point where this difference became significant we ran a point by point t-test (Guthrie and Buchwald 1991) between the cue and the probe, collapsed over probe type. The negative difference started to be significant ($p < 0.01$) at 60 ms in frontocentral electrodes (FCz, Cz, C2; Figure 5). At 120 ms, the significant negativity spread to more frontal electrodes, especially on the right, and later also to centroparietal electrodes (Figure 5). To validate the significance of the difference at the very early 60–80ms while accounting for the multiple comparisons across electrodes, we implemented SPM5, which provides a correction based on the random field theory (Kiebel & Friston, 2004; Kilner et al., 2005). At the first level analysis, the data was averaged across the 60 – 80 ms interval, for each subject. At the second level, a random effect analysis was conducted comparing Probe to Cue interpolated images using the F test. The corrected threshold for significance with family wise error = 0.05 was $F = 15.5$, with 3.1 resels. At this level, a fronto-central cluster was significantly different between conditions, congruent with the previous temporal analysis.

To better estimate the distribution of this differential activity along time, we computed the current source density (CSD) maps for the cue and probe conditions between 0 and 250 ms, by calculating the second spatial derivative of the voltage maps (Perrin et al., 1989; as implemented in Brain Vision Analyzer software, Brain Products, Germany). CSDs are less sensitive to far-field activity than voltage maps and therefore their peaks of activity are more circumscribed, and more likely to relate to immediately underlying cortical structures than voltage peaks (Srinivasan, 2005). The CSD of the difference between cue and probe

showed, around 60 ms post-onset, a complex pattern of right frontal and parieto occipital activations. A point by point t-test (Figure 6) was implemented comparing the CSDs elicited by the cue and probe stimuli across subjects, with the requirement that the difference reaches the $p < 0.01$ significance level for 8 consecutive time points, as dictated by the autocorrelation computed in the CSD data (Guthrie and Buchwald 1991). Figure 6 shows the distribution of t values passing the threshold, with a significant right frontal focus (at FC4) at the same time the potential difference starts to be significant (i.e., at around 60 ms). This activity is later joined by a left lateral frontal focus as well as a right occipito-temporal (PO8) activity[1].

In summary, compared to the cue, the probe elicited a significant negativity as soon as 60 ms post stimulus onset. This difference had a fronto-parieto-temporal distribution, but became significant earlier at right frontal sites than at posterior sites.

3. DISCUSSION

Theoretical models of prefrontal function (Miller & Cohen, 2000; Fuster, 1990) highlight its role in adaptively guiding perceptual and mnemonic mechanisms in a goal-directed manner. Critical to these executive control functions is the ability to flexibly process sensory inputs not solely based on their physical attributes, but also on their relevance within the behavioral context. In the current set of experiments, we measured regional timing indices across prefrontal and inferotemporal cortices to assess context-sensitive neural changes in the presence of identical bottom-up sensory input. We assessed both fMRI and ERP latency measures of neural activity in response to single face stimuli in two different contexts during a delayed recognition task: 1.) as novel tobe- remembered cue stimuli requiring mnemonic encoding processes, and 2.) as mnemonic probe stimuli which may or may not match a currently maintained face representation. Across these two mnemonic contexts, we report pronounced differentiation of neural processing of cue and probe face stimuli. These differences are consistent with a number of studies reporting context-dependent processing differences of identical sensory inputs (for examples, see Gazzaley et al., 2005; O'Craven et al., 1997).

In addition to an analysis of information processing differences across cue and probe stimuli, we also compared relative timing differences across frontal and posterior areas to index feedforward and feedback signals between regions. Our fMRI and EEG data replicate and extend previous fMRI and physiology evidence highlighting early retrieval-specific activity in the PFC (Druzgal & D'Esposito, 2003, Rainer et al., 1998) consistent with a top-down contribution of the PFC to memory-guided decision-making. Analysis of early temporal windows in EEG signals revealed rapid cue/probe differences in fronto-central electrodes as early as 60ms after stimulus onset – preceding evoked sensory signals peaking around 170ms in posterior electrodes thought to reflect facespecific perceptual responses in visual association cortex. This early sensitivity of frontal responses to the functional

[1]CSD differences were also found to be significant at lateral inferior frontal \ anterior temporal electrodes FT10 and FT9 from time 0 until 132 ms. This very early activity, which cannot be induced by the sample stimulus, could reflect anticipation. However, since this activity is seen at single electrodes at the very edge of the map, where the spatial derivative is less reliable, we do not discuss this further.

significance of bottom-up input places the PFC in a temporal window to control early sensory processing in a top-down manner.

Spatio-temporal Dynamics of Encoding and Retrieval Operations in WM

Several lines of neuroimaging and neurophysiology evidence suggest that the PFC is a key source of top-down mnemonic control signals during both WM encoding and retrieval operations. In the fMRI experiment, however, earlier time-to-peak (TTP) and time-to-onset (TTO) measures of the FFA response compared to the PFC at encoding suggests that neural activity in the PFC may be triggered after visual signals are already processed through visual association cortex. This would suggest that any PFC-mediated top-down influences to visual association cortex occur well after high-level visual processing in those regions. A consideration of our evidence within the context of previous neurophysiology work, however, suggests an alternative model of these interactions.

While a strict bottom-up flow is consistent with hierarchical models of visual processing which propose that sensory input must pass through several levels of processing before being relayed to higher order unimodal and heteromodal cortices (e.g. the PFC), recent latency information in neurophysiology responses challenges this strict serial flow of visual signals. Single-unit recording of FEF neurons (Schmolesky et al., 2000) and recordings from frontal electrodes in human ERPs (Foxe & Simpson, 2001) in response to passive viewing of visual stimuli report the onset of stimulus-driven responses in these regions within 70–80ms post-stimulus. These rapid visual signals in PFC are thought to be relayed via dorsal magnocellular projections (Schmolesky et al., 2000; Kveraga et al., 2007) concurrent in time with the first flow of basic signals through the ventral visual stream. This rapid signal propagation has been implicated as a feedforward trigger to the PFC allowing it to form rapid predictions about the visual world to selectively bias second-stage processing in ITC assemblies during object recognition (Bar, 2003). Other single-unit evidence reports later spiking latencies of face-selective PFC neurons at ~ 138ms (Scalaidhe et al., 1999) showing that even higher level stimulus-specific information about objects is relayed to the PFC in a sufficiently early window to influence later visual processing. These early feedforward signals through the visual system could trigger PFC mechanisms to guide strategic encoding by allocating attentional signals that can bolster later visual processing in ITC. Recent evidence highlighting shifts in the latency of the N170 response and an increase in fMRI activity to relevant vs. irrelevant faces at encoding (Gazzaley et al. 2005) shows that ITC activity is modulated by behavioral relevance.

While these rapid bottom-up visual signals to PFC are common at both encoding and retrieval stages in WM, our fMRI and EEG data reveals differences in the PFC across these two stages. During the retrieval stage of the delayed recognition tasks, subjects are required to compare probe stimuli with the content of representations being actively maintained in memory in order to make a binary memory decision. In a recent fMRI/EEG investigation of WM retrieval, Bledowski et al (2006) report a frontally distributed P300 response presumed to reflect the evaluation and comparison of stimuli following early N170 perceptual processes. While their analysis did not specifically focus on early evoked responses in frontal electrodes, our data reports the emergence of an early frontocentral negativity

(around 60ms) beginning not long after the first volley of visual signals reach V1 neurons at 30–50ms (Maunsell & Gibson, 1992) and remaining present throughout early stages of visual processing. This early negativity obtained with EEG, along with a relative shift in PFC and FFA fMRI latency measures, reflect context-dependent differences in PFC activity in the presence of identical bottom-up input. One potential model explaining these differences across stages is that while PFC receives early visual signals in response to both cue and probe faces, during memory retrieval there is an additional earlier PFC response which sums with the regular stimulus-driven activity to result in an earlier peak BOLD activity. Additional activity in memory-guided decision making is consistent with data showing an early spiking increase in response to target stimuli starting ~ 140ms (Thompson et al., 1997; Rainer et al., 1998; Freedman et al., 2003). Though these target-sensitivity measures are significantly later than the ~60ms window found in our EEG experiment, they reflect the time at which spiking to target stimuli diverges from non-targets, possibly after more elaborate processing, and not the absolute onset of neural activity in frontal neurons, which starts much earlier (cf. Thompson et al., 1997, Figure 2). Indeed, match vs. non-match divergence was found in our EEG study at a later stage as well (Figure 2). In conjunction with these neurophysiology measures, then, our data suggests a multidimensional role of the PFC in not just evaluation and decision-making at later stages (onwards from ~200 ms), but also place it in an early temporal position to guide early visual processing in a goal-directed manner.

While it is possible that the PFC monitors bottom-up signals in time to rapidly guide higher-level visual processing, another possible model is that the early probe-related activity reflects an expectancy signal. Given that our WM tasks had fixed delay period lengths, participants could have predicted the onset of the probe and engage anticipatory/preparatory processes. A wealth of electrophysiological findings have identified the Contingent Negative Variation (CNV) – an ERP component spanning the time window between one stimulus and another stimulus requiring a contingent response (Walter et al., 1964). Specifically, CNV patterns have been reported during delayed-recognition tasks in which the memory probe requires a response contingent upon the properties of the previous cue stimulus. It is unlikely however that the negativity reported for the probe stimulus here is due to a pre-stimulus baseline difference, as we measured the cue and the probe relative to their own pre-stimulus periods. Considering that the CNV evolves towards the probe, the probe pre-stimulus period was more negative, in absolute terms, then the cue pre-stimulus period. All other things being equal, subtracting this more negative baseline measure would have made the post-stimulus response to the probe seem more positive then the response to the cue - opposite of the observed results of Experiment 2. It is still possible, however, that in our fMRI and ERP findings, the early emergence of frontal activity is due to anticipatory processes continuing beyond the onset of the probe stimulus. Evidence further characterizing the later parts of the CNV has shown that it reflects neuronal excitability in the PFC (Fuster, 1990; Rockstroh et al., 1993) and is attenuated following dorsolateral PFC lesions (Rosahl & Knight, 1995). Importantly, whether the early activity observed in our experiments is triggered merely by the presence of the probe stimulus, in anticipation of it, or by an interaction between bottom-up information and an already excited population of neurons, these early differences across

memory operations are both consistent with the PFC biasing the posterior processing of the probe in a goal-directed manner.

Our data, then, are consistent with an early role of the PFC in modifying stimulus-processing based upon WM representations, but cannot conclusively determine the specific role of these early frontal signals or show a direct influence of them on IT processing. Within the context of delayed recognition tasks, these findings suggest that anticipatory processes or early visual information delivered to the PFC about the probe could initiate feedback signals to corresponding face-selective IT neurons. This feedback may serve to reactivate or bolster sustained memoranda-specific representations in favor of detecting matching incoming input. Consistent with this model, stimuli-selective IT neurons (Chelazzi et al., 1993) and the FFA (Druzgal & D'Esposito, 2001) exhibit enhanced responses to matching probe stimuli and corresponding increases are found in lateral PFC neurons in monkey experiments (Miller et al., 1996) and a region of the left MFG in a human fMRI experiment (Druzgal & D'Esposito, 2001).

Direct Evidence for PFC Involvement in Target Detection & Memory Retrieval

While it is known that PFC and ITC regions have rich reciprocal connectivity (Petrides and Pandya, 1999), without accompanying measures of functional connectivity, relative timing measures can only identify potential causal interactions rather than provide direct evidence for them (Miller & D'Esposito, 2005). Evidence assessing the effect of PFC lesions on posterior EEG signals (Yago et al., 2004; Barcelo & Knight, 2000) shows disruptions of rapid as well as sustained target-related sensory processing. PFC lesions lead to attenuation of target-related signals as early as 120–150ms and the disruptions persist throughout the 220ms time-window explored in our investigation and extend to interfere with later P3b target-sensitive responses. These direct measures highlighting the importance of early PFC feedback for the processing of targets are consistent with our data indicating early modulation of sensory signals based upon task relevance. Direct evidence for PFC-guided reactivation of representations in ITC was reported by Tomita et al. (1999) in an associative memory task. By employing a novel methodological strategy in which neural activity in inferotemporal cortex (ITC) was recorded following partial callosal resection, Tomita et al. were able to limit hemispheric crosstalk to the anterior corpus callosum connecting between the prefrontal cortices. When a cue stimulus was delivered to the visual field ipsilateral to the recording site, thus restricting bottom-up visual processing to the opposite hemisphere, neurons at the recording site exhibited stimulus-selective activity 170ms later. The fact that these neurons received no bottom-up visual signals and the only route between the hemispheres was via the PFC provides strong evidence that the PFC is sufficient to send top-down reactivation signals to enhance task-relevant representations in ITC.

Latency-Resolved fMRI: Is it time?

Since fMRI can almost simultaneously record hemodynamic signals from the whole brain with millimeter resolution, it is in a unique position to track bottom-up and top-down interactions between specific subregions of cortex. Traditionally limited because it measures a sluggish hemodynamic correlate of neural activity, recent design and analysis tools have increased the sensitivity of fMRI to measure the onset of neural signals in the brain. Menon

et al (1998) first reported that when a right hemifield checkerboard was presented and followed 125ms later by a left hemifield checkerboard, the TTO and TTP of the BOLD signal tracked this stimulus presentation pattern with activity in right V1 following that in left V1 by the predicted interval.

Latency-resolved fMRI becomes a greater challenge, however, as experiments attempt to investigate more complex cognitive operations involving interactions between distributed neural systems. Due to regional differences in vascular supply, it is difficult to map regional timing measures in fMRI directly back onto the underlying neurophysiology since these measures could instead be artifacts of regional variation in baseline vascular responses (Buckner, 2003). In order to address the spatio-temporal dynamics of distributed networks, recent methodological advancements and design strategies have focused on improving control over regional differences in baseline hemodynamics. One strategy has been to correlate BOLD timing parameters with overt behavioral measures such as reaction time to get a direct link between the timing of a region's response and its effects on behavior (Menon et al., 1998; Formisano & Goebel, 2002). Another promising design strategy, employed in our fMRI experiment, is to hold bottom-up sensory input constant across two cognitive operations that are presumed to engage similar cortical networks. By perturbing the network in the same manner and assessing context-sensitive changes in temporal measures, it is possible to detect systematic changes in temporal parameters across the brain. Bellgowan, Saad & Bandettini (2003) used a similar strategy that manipulates the duration of a cognitive process by rotating word stimuli and showing a slowing of neural activity in the inferior frontal gyrus that corresponded to the extent of the word rotation. This gradual increase in onset latency reflects a context-dependent delay in physiological response that is due to a manipulation of cognitive context.

Improvements in the temporal sensitivity of fMRI have also been driven by advances in modeling and analytical techniques. Similar to the model-fitting algorithm employed in the current study, these techniques have allowed fMRI to detect regional differences in the BOLD response at sub-sampling temporal resolution. For example, a recent investigation (Sigman et al., 2007) employed a visuo-motor task with periodic synchronicity to extract 100ms level timing differences across regions. They utilized a novel analysis strategy in which power and phase spectral features of the response were examined to track temporal information. Other recent investigations have applied coherence phase measures (Sun et al., 2005; Sun et al., 2007), information theory (Fuhrmann Alpert et al., 2007), and granger causality (Goebel et al., 2003; Abler et al., 2006) to push fMRI temporal sensitivity to new levels.

Though these strategies have enhanced the ability of fMRI to shed light on the temporal cascade of neural activity across the brain, several technical considerations must be taken into account when interpreting latency-resolved fMRI measures. One initial challenge for addressing timing differences across subcomponent operations in a complex cognitive task is the ability to obtain separate estimates for stage-specific neural responses. In our fMRI experiment, we utilized a partial-trial design (Ollinger et al., 2000) to isolate the stage-specific waveforms of the fMRI BOLD signal in PFC, IPS, and FFA regions of interest. Our design was directly aimed at overcoming the obstacles inherent to any investigation trying to

tease apart stage-specific fMRI activity patterns during a WM task. Given the necessarily close temporal proximity and the invariant order of the three stages of a delayed recognition task (e.g. cue, delay, probe), BOLD signals reflecting neural activity specific to encoding, maintenance, and retrieval/response operations overlap in the sluggishly evolving BOLD response. One methodological technique to parcel out stage-specific variance in the fMRI signal is to model each stage with a series of time-shifted covariates in the form of an assumed hemodynamic response function (HRF) (Zarahn, Aguirre, D'Esposito, 1997). While these models have been used in many fMRI analyses of WM tasks, they are extremely sensitive to the shape of the assumed BOLD response which has been shown to vary across individuals and brain regions (Miezin et al., 2000; Handwerker & D'Esposito, 2004). Manoach et al. (2003) addressed this shortcoming by employing the same FIR approach used in our study which makes no a priori assumptions about the shape of the BOLD response across regions. Given their aim of detecting regions commonly or selectively engaged across subcomponent stages, they applied the finite impulse response (FIR) model to the entire WM trial epoch and based statistical comparisons on particular time points in the overall signal presumed to maximally reflect specific stages. With the inclusion of catch trials (Ollinger et al., 2000), the present experiment avoided this a priori mental deconvolution approach in which fMRI signal at certain timepoints is assumed to maximally reflect neural processing related to specific temporally-segregated events.

Another primary methodological consideration of latency-resolved fMRI is mapping hemodynamic timing measures back onto the underlying neurophysiological activity – a challenge referred to as the 'hemodynamic inverse problem' (Buckner, 2003). In order to use temporal characteristics of neural responses as indices of potential effective connectivity between the PFC and FFA, it would be ideal to obtain measures showing that activity in a presumed source of top-down feedback (i.e. PFC) precedes activity in hypothesized sites of top-down effects (e.g. FFA). While the time-to-peak (TTP) measurements of the left MFG response preceded the peak of the FFA response at retrieval, these measurements are sensitive not only to the latency but also to the duration of regional neural activity (Henson et al., 2002). As a result, two regions with identical onset times of neural activity can have significantly different TTP measures in the BOLD signal depending upon the duration of neural activity across the regions. Thus, while the relative latency shift of the PFC and FFA time-courses in our fMRI experiment is consistent with an early contribution of the PFC in guiding recognition memory decisions (and perhaps directly influencing perceptual processing in the FFA), another plausible explanation is that the shift in relative timing between the MFG and FFA at the probe could be driven by either by a shorter duration of MFG activity or a longer duration of FFA activity in response to the probe stimulus compared to the cue stimulus.

The sensitivity of the BOLD hemodynamic signal to the duration of neural activity may also be the source of one incongruity across techniques in this investigation. While Experiment 1 highlighted voxels specific to the *left* MFG that had an earlier TTP across stages in the BOLD signal (there were no significant differences in right MFG relative to the FFA), experiment 2 reports the earliest divergence of retrieval and encoding electrophysiology signals in electrodes over the *right* frontal electrodes. Though left frontal electrodes

followed quickly after those on the right, this hemispheric asymmetry across techniques may be explained by differences in the duration of activity across right and left frontal regions that can artificially alter TTP measures in these regions. A post-hoc analysis assessing the duration of this significant activity revealed that electrodes over the right hemisphere showed a trend toward a longer duration of significant negativity in the ERP response. Though purely speculative at this point, this electrophysiology data may reflect early bilateral activity in the PFC at retrieval that is missed in the fMRI data due to hemispheric differences in the duration of neural activity during the memory-guided decision making process.

Joint Methodology Approach: ERP insights

Though latency-resolved fMRI offers the advantage of obtaining temporal measures with high spatial specificity, complementary ERP evidence provides a unique ability to supplement regional hemodynamic timing information with millisecond-resolution temporal measures. In the present case, the finding of a shift in latency of activity in frontal cortices relative to temporal cortices between cue and probe processing (Druzgal & D'Esposito, 2003) directly motivated the ERP study, attempting to elucidate the mechanism leading to this shift in the BOLD response. By using ERPs, we could accurately track the time point at which responses to cue and probe stimuli, which were physically similar, differed. By using a relatively dense array of electrodes, we could also determine the spatio-temporal dynamics of this differential response on the scalp. However, because of volume conduction, scalp electrodes reflect activity from remote regions of the brain and thus the distribution of potentials across the scalp cannot unambiguously resolve the intracranial electrical source location - a problem known as the 'inverse' problem (the forward being the projection of intracranial sources to the scalp). This is because the number of possible configurations of active electrical sources in the brain and their momentary amplitudes far exceeds the number of electrodes, making the problem ill-posed mathematically. Thus, merging data from EEG and fMRI not only gains from the complementary advantages of the methods, but also suffers from their complementary disadvantages: a well localized active focus in fMRI could reflect neural activity at any time within the first second after the stimulus onset, and so it is hard to associate it with a given ERP component, which is limited in time but spatially ambiguous.

Several methods have been proposed for approximating an inverse solution based on various constraints which are based on often arbitrary a-priori assumptions (see Michel et al., 2004 for review). Rather than trying to precisely localize the encoding/retrieval effect in the brain by using inverse solutions, we chose to use the CSD (Laplacian) method which has no a priori constraints and is independent of the EEG reference site (Perrin et al., 1989). By practically implementing a spatial high-pass filter over the potential map, CSD peaks are more likely related to immediately underlying cortical structures than corresponding voltage peaks, especially in the crest of gyri (Srinivasan, 2005). This analysis suggested the earliest differences between encoding and retrieval are related to activity in prefrontal regions. Previous EEG studies (Foxe & Simpson, 2002) as well as intracranial recordings in humans (Blanke et al., 1999) and monkeys (see Lamme & Roelfsema, 2000 for review) reveal that the timing of this activity, onwards from 60 ms, matches the time at which visual

information reaches the frontal cortex. In contrast, we did not find any effect of the stage of the trial on the face-specific N170 electrical response, whereas BOLD latency effects were found in the FFA. However, although both N170 and FFA activity reflect face sensitive processing, there is evidence that they are distinct (Shibata et al., 2002; Itier et al., 2007). For example, patients with congenital prosopagnosia show no N170 specificity for faces but show a normal FFA specificity (Bentin et al., 1999; DeGutis et al., In press; Hasson et al., 2003).

Conclusion

In the present set of experiments we provide fMRI and ERP evidence consistent with differences in the neural mechanisms underlying encoding and retrieval operations in WM. This combination of evidence from two complementary cognitive neuroscience methods offers a unique opportunity to characterize the spatio-temporal dynamics of cortical networks involved in WM. In experiment 1, an analysis of stage-specific latency measures in BOLD fMRI revealed a context-dependent shift in PFC/ITC relative latencies across encoding and retrieval. While relative timing measures in the FFA lead those of the PFC at encoding, the PFC response at retrieval exhibited an earlier time-to-peak than the FFA. These stage-specific temporal differences suggest differential involvement of frontal regions across WM operations and highlight PFC activity in a temporal window early enough to perform a role in the top-down guidance of strategic encoding and of memory-guided decision making. In experiment 2, a focused analysis of the first 220ms of the ERP response across stages revealed a rapid differentiation of encoding and retrieval signals beginning as early as 60ms post-stimulus. These rapid differences in neural mechanisms in the presence of identical bottom-up sensory input are consistent with theoretical models and other physiology evidence implicating the PFC as a key source of modulatory signals to bias sensory processing in a top-down manner.

4.) Experimental Procedure

Experiment 1

Behavioral Procedure—The participants in this study were seven 19–24 (M = 21.3) year-old students (3 female) from the University of California at Berkeley. All participants were right handed with normal or corrected-to-normal vision and none reported any history of neurological or psychiatric problems. Each participant gave informed written consent prior to being tested and received monetary compensation upon completion of the study. The following experimental procedure was conducted in compliance with the Committee for the Protection of Human Subjects at the University of California, Berkeley.

Prior to the main experimental behavioral task, participants performed a task with blocks of face and scene stimuli. This data was utilized to functionally localize fusiform face area (FFA) regions of interest (see statistical methods). Participants viewed 16 second blocks of 20 face or 20 scene stimuli presented for 300ms each with a 500ms ITI. To ensure that participants were viewing the stimuli, they were instructed to make a button-press with their right index finger any time that an image matched the image immediately preceding it.

There were seven blocks of each category of stimuli and the localizer run lasted 5 min 45 seconds.

Following this run, participants performed seven runs of a delayed-recognition WM task with face stimuli. A set of 360 grayscale photographs of human faces with neutral expressions was assembled. Several steps were taken to promote the use of face recognition, rather then recognition of extrinsic features. Image processing was carried out using Adobe Photoshop (version 6.0). All external features, such as hair, ears and the background of the photograph, were cropped from the picture and replaced by a gray background. The boundary between the face and the background was then blurred by using the Photoshop “smudge” tool. For matching pairs, the actual position of the face within the image was altered slightly for one of the images in the pair, and its brightness was slightly changed. Thus, although the cue and probe faces in match trials were the same, the cue and probe images were not physically identical. All images were 174 × 232 pixels with a resolution of 72 DPI.

The main trial type of interest in this task was a "full" delayed-recognition face WM task. A single face memory cue was presented for 500ms followed by a brief 1500ms delay period marked by a centrally presented fixation cross. To test for successful memory encoding and maintenance, a 500ms probe face was presented and the subject indicated with a button-press whether the probe face matched the cue stimulus. Following the design strategy of Ollinger et al. (2001) aimed at separately estimating contiguous stages of a multi-stage task, two other partial trial types were included. These partial trials are designed to elicit a subset of the cognitive processes involved in the full WM trial and, consequently, a subset of the fMRI response. Two partial trial types were used: 1) a “cue+delay” partial trial in which the 500ms cue face is followed by a fixation cross during a 1500ms delay before the offset of the fixation cross indicating the end of the trial and 2) a “cue_only” partial trial in which the 500ms face cue stimulus is not followed by a fixation cross indicating the end of the trial. Importantly, these two partial trial conditions were randomly intermixed with the other trial types to ensure that participants could not predict the nature of the upcoming trial. A fourth trial type was structured identical to the “full” WM trials except that instead of a face memory probe, the fixation cross turned either red or green and the participants indicated the color with an index or middle finger button press, respectively. These trials were not included in the current analyses. Jittered inter-trial intervals (ITI) (50% 4s, 25% 6s, 25% 8s) were used to maximize efficiency of response estimation. Each run was composed of 40 trials and lasted 6.5min.

MRI acquisition and pre-processing—Functional images were acquired from a Varian INOVA 4 Tesla scanner equipped with a transverse electromagnetic (TEM) send-and-receive radio frequency (RF) head coil. Functional images were collected using a gradient echoplanar sequence (TR = 2000 ms, TE = 28 ms, matrix size = 64 × 64, FOV = 22.4 cm) sensitive to BOLD contrast. Each functional volume consisted of 18 × 5 mm thick axial slices with 0.5 mm gap between each slice, providing whole brain coverage except for portions of the inferior cerebellum and the most superior extent of the parietal lobe. For each scan, ten seconds of gradient and RF pulses preceded data acquisition to allow steady-state tissue magnetization. Two T1-weighted anatomical scans were also acquired. In the first,

anatomical images coplanar with the EPI data were collected using a gradient-echo multislice (GEMS) sequence (TR = 200 msec, TE = 5 msec, FOV = 22.4 cm2, matrix size = 256 × 256, in-plane resolution = 0.875 × 0.875 mm). These images were used in later analyses to determine individual-specific regions of interest as well as to anatomically localize functional activations. In the second, high-resolution anatomical data were acquired with an MP-FLASH 3-D sequence (TR = 9 msec, TE = 5 msec, FOV = 22.4 × 22.4 × 19.8 cm, matrix size = 256 × 256 × 128, resolution = 0.875 × 0.875 × 1.54 mm).

Following acquisition, MRI data were converted to ANALYZE format. Data were corrected for between-slice timing differences using a sinc interpolation method and were interpolated to 1-sec temporal resolution (half of the total repetition time) by combining each shot of half k space with the bilinear interpolation of the two flanking shots. Subsequent preprocessing and statistical analysis were performed using SPM2 software http://www.fil.ion.ucl.ac.uk) run under Matlab 6.5 (www.mathworks.com). Functional data were realigned to the first volume acquired. To optimize estimation of voxel-wise time-series waveforms, no spatial smoothing kernel was applied to the data.

Statistical Methods

Localization of Fusiform Face Area (FFA) ROIs: BOLD responses to blocks of face and scene stimuli in the localization task were modeled with 16s regressors convolved with a canonical HRF in a standard general linear model (GLM) analysis. Following parameter estimation, a contrast of face stimuli vs. scene stimuli was computed and voxels within each participant's fusiform gyrus that were significantly more active to faces than scenes ($p<.0001$, uncorrected) were used as FFA ROIs.

Localization of PFC ROIs: Regions in the PFC that were significantly engaged in the WM task were isolated using a combined anatomical and functional isolation approach. Anatomical ROIs were drawn on each individual participant's coplanar anatomical scan for right and left dorsolateral PFC (middle frontal gyrus – MFG) and bilateral ventrolateral PFC (inferior frontal gyrus – IFG). To isolate activated voxels, an independent GLM was computed for each condition type ("full", "cue+delay", and "cue"). Parameter estimates for the "full" trial were compared to unmodeled baseline composed of null intervals in the ITI to extract voxels significantly ($p<.0001$, uncorrected) activated by the WM trials. The anatomical ROIs were then used as masks on the functional maps to extract the subset of significant voxels within each anatomical ROI for subsequent time-series analysis. Extracted voxels in more ventral ROIs were less consistent across subjects (with some subjects revealing no suprathreshold voxels) so these were not included in further temporal analyses.

Model estimation with finite impulse response (FIR) function: For each participant, time-series waveforms across the entire brain were estimated for each voxel by applying a linear regression model capable of separately computing time courses for the encoding stage (e.g. presentation of the cue) and the retrieval stage (e.g. presentation of the probe) without making assumptions about the shape of the hemodynamic response (Ollinger et al., 2001; Kinkade et al., 2005). In the design matrix, each trial was coded by sixteen delta functions in the following manner. The cue_only and cue+delay partial trials were coded in the design

matrix as two different conditions each with a set of 16 delta functions starting at the TR of cue onset. The full WM trials were coded as a mixed trial starting with 16 delta functions coding a cue+delay trial followed 2TRs later by 16 more delta functions coding for the retrieval event. In this case, the presence of cue+delay partial trials allows for an accurate modeling of the time-series in response to the retrieval stimulus (Ollinger et al., 2001). Estimation of the design matrices led to one 16s time-series waveform for each condition (cue_only, cue_delay, probe) for each voxel.

Extraction of timecourses and estimation of temporal parameters: Following estimation of the regression model, time-series estimates within the voxels of each ROI were averaged to obtain averaged waveforms for the encoding and retrieval conditions in the FFA and PFC ROIs. The averaged 16s timecourses for the cue_only and retrieval conditions were then used to calculate time-to-onset and time-to-peak measures of the BOLD response for cue and probe periods, respectively, in each region. To estimate these parameters, the waveforms were fit with a model composed of the sum of two gamma functions aimed at minimizing the residual between the model and the actual timecourses (Meizin et al., 1999). The model fitting upsampled the temporal resolution of the waveforms by a factor of four and used a best fit estimation to determine time-to-onset and time-to-peak measures. Two features of these timing measures were then statistically compared using t-tests. The first was within stage (e.g. cue or probe) relative timing differences across regions in order to measure the relative timing of FFA and PFC during encoding and retrieval processing stages. The second was the within-region difference in temporal parameters across the cue and probe periods. The latter measures assess how the temporal properties of an area's activity differ across encoding and retrieval.

Experiment 2

Behavioral Procedure—The participants in this study were fifteen 18–25 (M = 21.4 +/− 2.4) year-old students (9 female) from the University of California at Berkeley. All participants were right handed with normal or corrected-to-normal vision and none reported any history of neurological or psychiatric problems. Each participant gave informed written consent prior to being tested and received monetary compensation upon completion of the study. The following experimental procedure was conducted in compliance with the Committee for the Protection of Human Subjects at the University of California, Berkeley.

Participants were seated in a reclining armchair in a darkened, sound attenuated and electrically shielded chamber. Stimuli were presented, using E-prime software (version 1.0, Psychology Testing Tools), on a 21-inch CRT monitor located approximately 1 m from the participants. Participants were instructed to fixate centrally and to minimize unnecessary movements.

The participants conducted a delayed recognition WM task composed of three blocks. A total of 120 matching and 120 non-matching face pairs as well as 48 catch trials (non-face objects such as furniture, cars and houses) were presented. The catch trials were randomly presented at 1/6 probability and required no response. During each WM (i.e. face-pair) trial, a cue face was presented for 100 ms followed by a 2 second delay. A probe face was then

presented for 100 ms. Half of the probe images were of the same face as in the cue image, and half of a different face. Participants were instructed to passively view the cue face and to "hold it in their mind" during the 2 second delay (marked with a fixation cross). When the probe face appeared, they were instructed to decide if this second face was the same (a match) or different (a nonmatch). On half of the trials, the participants had to press a button in case of a matching probe and withhold response otherwise (Go for Match trial), and vice versa in the other half (Go for Non-Match trials). The response instruction ("PRESS NOW FOR MATCH" or "PRESS NOW FOR NON MATCH") appeared a variable 1-1.5s *after* the onset of the probe. This design allowed us to separate the motor preparation potentials (starting following the response instruction) from the potentials related to perception and decision time-locked to the probe. The response window of 1500 ms was followed by a variable inter-trial interval of 1000–2000 ms. Stimuli were obtained from the same set of 360 grayscale faces used in Experiment 1.

EEG Recording—The EEG was recorded from 63 tin electrodes, including four electro-oculography (EOG) electrodes, referenced to a nose electrode. Vertical eye movements were monitored by EOG electrodes placed above and below the right eye and horizontal eye movements were monitored by EOG electrodes placed at the outer canthus of each eye. Scalp electrodes were placed according to a modified 10–20 system (Electro-cap). The EEG was sampled at 250 Hz (Keithley DAS-1802HC Metrabyte AD card controlled by Neuroscan 4.1, Sterling, VA), amplified by 20,000 with an analog band pass filter of 0.1 to 30 Hz (SA Instrumentation, San Diego, CA) and stored for off-line analysis. Post processing of the data was done with Brain Vision Analyzer (Version 1.05, Brain Products, München, Germany). The EEG data was parsed into 1100 ms epochs, starting 100 ms prior to stimulus onset. Trials contaminated by blinks, eye movements, gross muscle movements and excessive noise were rejected. These artifacts were detected by setting a maximum allowed amplitude of ±100μV. Blinks and saccades were further detected on vertical and horizontal EOG bipolar derivations by setting a maximum allowed amplitude based on the magnitude of the subjects' observable blinks and saccades. No more than 1/3 of trials were rejected in any subject. The epochs were then averaged separately for each stimulus type, referenced to the average pre-stimulus baseline period, and digitally filtered with a band-pass of 0.5 –20 Hz. Only trials with correct responses were considered. The predefined face-sensitive components N170 and VPP (Bentin et al., 1996;Jeffreys, 1989; Itier & Taylor, 2002) were measured as the average of 5 data points (20 ms) centered on the peak latency, as determined on the grand average waveform. Point by point 2-tailed paired t-tests were conducted comparing cue to probe waveforms within the first 0–220 ms after stimulus onset. To control for inflated type I error due to multiple comparisons, the t-test was required to pass a predefined threshold for 12 sequential time points to be considered significant (Guthrie & Buchwald, 1991). This number of time points was chosen following computation of the autocorrelation in the filtered data, based on the procedure suggested by Guthrie and Buchwald.

SPM5 supplemental analysis—EEG images were created by spline interpolating the data, using a grid of 58 by 58 pixels (SPM5, http://www.fil.ion.ucl.ac.uk/spm/). At the first-level analysis, the average of the 60–80 ms epoch was calculated for each subject for the cue

and probe stimuli separately. At the second level, a GLM random-effect analysis was performed contrasting cue and probe across the subjects to create Fstatistic statistical parametric maps, where an F value is computed for each pixel. An F threshold adequate for family-wise error of 0.05 at the voxel level was calculated based on random field theory (Kiebel & Friston, 2004; Kilner et al., 2005).

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References

Abler B, Roebroeck A, Goebel R, Höse A, Schönfeldt-Lecuona C, Hole G, Walter H. Investigating directed influences between activated brain areas in a motor-response task using fMRI. Magn Reson Imaging. 2006; 24(2):181–185. [PubMed: 16455407]

Bar M. A cortical mechanism for triggering top-down facilitation in visual object recognition. J Cogn Neurosci. 2003; 15(4):600–609. [PubMed: 12803970]

Barcelo F, Suwazono S, Knight RT. Prefrontal modulation of visual processing in humans. Nat Neurosci. 2000; 3(4):399–403. [PubMed: 10725931]

Bauer RH, Fuster JM. Delayed-matching and delayed-response deficit from cooling dorsolateral prefrontal cortex in monkeys. J Comp Physiol Psychol. 90(3):293–302. [PubMed: 819472]

Bellgowan PS, Saad ZS, Bandettini PA. Understanding neural system dynamics through task modulation and measurement of functional MRI amplitude, latency, and width. Proc Natl Acad Sci U S A. 2003; 100(3):1415–1419. [PubMed: 12552093]

Bentin S, McCarthy G, Perez E, Puce A, Allison T. Electrophysiological studies of face perception in humans. Journal of Cognitive Neuroscience. 1996; 8:551–565. [PubMed: 20740065]

Bentin S, Deouell LY, Soroker N. Selective visual streaming in face recognition: evidence from developmental prosopagnosia. NeuroReport. 1999; 10:823–827. [PubMed: 10208555]

Blanke O, Morand S, Thut G, Michel CM, Spinelli L, Landis T, Seeck M. Visual activity in the human frontal eye field. NeuroReport. 1999; 10:925–930. [PubMed: 10321461]

Bledowski C, Cohen Kadosh K, Wibral M, Rahm B, Bittner RA, Hoechstetter K, Scherq M, Maurer K, Goebel R, Linden DE. Mental chronometry of working memory retrieval: a combined functional magnetic resonance imaging and event-related potentials approach. J Neurosci. 2006; 26(3):821–829. [PubMed: 16421302]

Buckner RL. The hemodynamic inverse problem: making inferences about neural activity from measured MRI signals. Proc Natl Acad Sci U S A. 2003; 100(5):2177–2179. [PubMed: 12606715]

Buschman TJ, Miller EK. Top-down versus bottom-up control of attention in the prefrontal and posterior parietal cortices. Science. 2007; 315(5820):1860–1862. [PubMed: 17395832]

Chelazzi L, Miller EK, Duncan J, Desimone R. A neural basis for visual search in inferior temporal cortex. Nature. 1993; 363(6427):345–347. [PubMed: 8497317]

Curtis CE, D'Esposito M. Persistent activity in the prefrontal cortex during working memory. Trends Cogn Sci. 2003; 7(9):415–423. [PubMed: 12963473]

DeGutis JM, Bentin S, Robertson LC, D'Esposito M. Functional plasticity in ventral temporal cortex following cognitive rehabilitation of a congenital prosopagnosic. J Cogn Neurosci. 2007; 19(11): 1790–1802. [PubMed: 17958482]

D'Esposito M, Ballard D, Zarahn E, Aguirre GK. The role of prefrontal cortex in sensory memory and motor preparation: an event-related fMRI study. Neuroimage. 2000; 11(5):400–408. [PubMed: 10806027]

Druzgal TJ, D'Esposito M. A neural network reflecting decisions about human faces. Neuron. 2001; 32(5):947–955. [PubMed: 11738037]

Druzgal TJ, D'Esposito M. Dissecting contributions of prefrontal cortex and fusiform face area to working memory. 2003; 15(6):771–784.

Formisano E, Linden DE, Di Salle F, Trojano L, Esposito F, Sack AT, Grossi D, Zanella FE, Goebel R. Tracking the mind's image in the brain I: time-resolved fMRI during visuospatial mental imagery. Neuron. 2002; 35(1):185–194. [PubMed: 12123618]

Foxe JJ, Simpson GV. Flow of activation from V1 to frontal cortex in humans - A framework for defining "early" visual processing. Experimental Brain Research. 2002; 142:139–150. [PubMed: 11797091]

Freedman DJ, Riesenhuber M, Poggio T, Miller EK. A comparison of primate prefrontal and inferior temporal cortices during visual categorization. J Neurosci. 2003; 23(12):5235–5246. [PubMed: 12832548]

Fuhrmann Alpert G, Sun FT, Handwerker D, D'Esposito M, Knight RT. Spatio-temporal information analysis of event-related BOLD responses. Neuroimage. 2007; 34(4):1545–1561. [PubMed: 17188515]

Funahashi S, Bruce CJ, Goldman-Rakics PS. Mnemonic coding of visual space in the monkey's dorsolateral prefrontal cortex. J. Neurophysiol. 1989; 61(2):331–349. [PubMed: 2918358]

Funahashi S, Bruce CJ, Goldman-Rakic PS. Dorsolateral prefrontal lesions and oculomotor delayed-response performance: evidence for mnemonic "scotomas". J Neurosci. 1993; 13(4):1479–1497. [PubMed: 8463830]

Fuster JM, Alexander GE. Neuron activity related to short-term memory. Science. 1971; 173(997): 652–654. [PubMed: 4998337]

Fuster JM, Bauer RH, Jervey JP. Functional interactions between inferotemporal and prefrontal cortex in a cognitive task. Brain Res. 1985; 330(2):299–307. [PubMed: 3986545]

Fuster JM. Prefrontal cortex and the bridging of temporal gaps in the perception-action cycle. Ann N Y Acad Sci. 1990; 608:318–329. [PubMed: 2127512]

Fuster JM. Network Memory. Trends Neurosci. 1997; 20(10):451–459. [PubMed: 9347612]

Gazzaley A, Cooney JW, McEvoy K, Knight RT, D'Esposito M. Top-down enhancement and suppression of the magnitude and speed of neural activity. J Cogn Neurosci. 2005; 17(3):507–517. [PubMed: 15814009]

Goebel R, Roebroeck A, Kim DS, Formisano E. Investigating directed cortical interactions in time-resolved fMRI data using vector autoregressive modeling and Granger causality mapping. Magn Reson Imaging. 2003; 21(10):1251–1261. [PubMed: 14725933]

Guthrie D, Buchwald JS. Significance testing of difference potentials. Psychophysiology. 1991; 28:240–244. [PubMed: 1946890]

Handwerker DA, Ollinger JM, D'Esposito M. Variation of BOLD hemodynamic responses across subjects and brain regions and their effects on statistical analyses. Neuroimage. 2004; 21(4):1639–1651. [PubMed: 15050587]

Hasson U, Avidan G, Deouell LY, Bentin S, Malach R. Face-selective activation in a congenital prosopagnosic subject. J Cogn Neurosci. 2003; 15:419–431. [PubMed: 12729493]

Henson RN, Price CJ, Rugg MD, Turner R, Friston KJ. Detecting latency differences in event-related BOLD responses: application to words versus nonwords and initial versus repeated face presentations. Neuroimage. 2002; 15(1):83–97. [PubMed: 11771976]

Itier RJ, Taylor MJ. Inversion and Contrast Polarity Reversal Affect both Encoding and Recognition Processes of Unfamiliar Faces: A Repetition Study Using ERPs. NeuroImage. 2002; 15:353. [PubMed: 11798271]

Jeffreys DA. A face-responsive potential recorded from the human scalp. Experimental Brain Research. 1989; 78:193. [PubMed: 2591512]

Jha AP, McCarthy G. The influence of memory load upon delay-interval activity in a working-memory task: an event-related functional MRI study. J Cogn Neurosci. 2000; 12(Suppl 2):90–105. [PubMed: 11506650]

Joyce C, Rossion B. The face-sensitive N170 and VPP components manifest the same brain processes: The effect of reference electrode site. Clinical Neurophysiology. 2005; 116:2613. [PubMed: 16214404]

Kiebel SJ, Friston KJ. Statistical parametric mapping for event-related potentials: I. Generic considerations. Neuroimage. 2004; 22:492–502. [PubMed: 15193578]

Kilner JM, Kiebel SJ, Friston KJ. Applications of random field theory to electrophysiology. Neuroscience Letters. 2005; 374:174–178. [PubMed: 15663957]

Kincade JM, Abrams RA, Astafiev SV, Shulman GL, Corbetta M. An event-related functional magnetic resonance imaging study of voluntary and stimulus-driven orienting of attention. J Neurosci. 2005; 25(18):4593–4604. [PubMed: 15872107]

Kubota K, Niki H. Prefrontal cortical unit activity and delayed alternation performance in monkeys. J. Neurophysiol. 1971; 34(3):337–347. [PubMed: 4997822]

Kveraga K, Boshyan J, Bar M. Magnocellular projections as the trigger of top-down facilitation in recognition. J Neurosci. 2007; 27(48):13232–13240. [PubMed: 18045917]

Lamme VAF, Roelfsema PR. The distinct modes of vision offered by feedforward and recurrent processing. Trends Neurosci. 2000; 23:571–579. [PubMed: 11074267]

Manoach DS, Greve DN, Lindgren KA, Dale AM. Identifying regional activity associated with temporally separated components of working memory using event-related functional MRI. Neuroimage. 2003; 20(3):1670–1684. [PubMed: 14642477]

Maunsell JH, Gibson JR. Visual response latencies in striate cortex of the macaque monkey. J Neurophysiol. 1992; 68(4):1332–1344. [PubMed: 1432087]

Menon RS, Luknowsky DC, Gati JS. Mental chronometry using latency-resolved fMRI. Proc Natl Acad Sci USA. 1998; 95(18):10902–10907. [PubMed: 9724802]

Michel CM, Murray MM, Lantz G, Gonzalez S, Spinelli L, Grave de Peralta R. EEG source imaging. Clin Neurophys. 2004; 115:2195–2222.

Miezin FM, Maccotta L, Ollinger JM, Petersen SE, Buckner RL. Characterizing the hemodynamic response: effects of presentation rate, sampling procedure, and the possibility of ordering brain activity based on relative timing. Neuroimage. 2000; 11(6):735–759. [PubMed: 10860799]

Miller BT, D'Esposito M. Searching for 'the top' in top-down control. Neuron. 2005; 48(4):535–538. [PubMed: 16301170]

Miller EK, Erickson CA, Desimone R. Neural mechanisms of visual working memory in prefrontal cortex of the macaque. J Neurosci. 1996; 16(16):5154–5167. [PubMed: 8756444]

Miller EK, Cohen JD. An integrative theory of prefrontal cortex function. Annu Rev Neurosci. 2001; 24:167–202. [PubMed: 11283309]

Muhammad R, Wallis JD, Miller EK. A comparison of abstract rules in the prefrontal cortex, premotor cortex, inferior temporal cortex, and striatum. J Cogn Neurosci. 2006; 18(6):974–989. [PubMed: 16839304]

O'Craven KM, Rosen BR, Kwong KK, Treisman A, Savoy RL. Voluntary attention modulates fMRI activity in human MT-MST. Neuron. 1997; 18(4):591–598. [PubMed: 9136768]

Ollinger JM, Shulman GL, Corbetta M. Separating processes within a trial in event-related functional MRI. Neuroimage. 13(1):210–217. [PubMed: 11133323]

Ollinger JM, Corbetta M, Shulman GL. Separating processes within a trial in event-related functional MRI. Neuroimage. 2001; 13(1):218–229. [PubMed: 11133324]

Perrin F, Pernier J, Bertrand O, Echallier JF. Spherical splines for scalp potential and current density mapping. Electroencephalogr Clin Neurophysiol. 1989; 72:184–187. [PubMed: 2464490]

Pessoa L, Gutierrez E, Bandettini P, Ungerleider L. Neural correlates of visual working memory: fMRI amplitude predicts task performance. Neuron. 2002; 35(5):975–987. [PubMed: 12372290]

Petrides M, Pandya DN. Dorsolateral prefrontal cortex: comparative cytoarchitectonic analysis in the human and the macaque brain and corticocortical connection patterns. Eur J Neurosci. 1999; 11(3):1011–1036. [PubMed: 10103094]

Philiastides MG, Sajda P. Temporal characterization of the neural correlates of perceptual decision making in the human brain. Cerebral Cortex. 2006; 16:509. [PubMed: 16014865]

Quintana J, Fuster JM. Spatial and temporal factors in the role of prefrontal and parietal cortex in visuomotor integration. Cereb Cortex. 1993; 3(2):122–132. [PubMed: 8490318]

Rainer G, Asaad WF, Miller EK. Memory fields of neurons in the primate prefrontal cortex. Proc Natl Acad Sci U S A. 1998; 95(25):15008–15013. [PubMed: 9844006]

Ritter P, Villringer A. Simultaneous EEG-fMRI. Neurosci Biobehav Rev. 2006; 30:823–838. [PubMed: 16911826]

Rockstroh B, Müller M, Wagner M, Cohen R, Elbert T. "Probing" the nature of the CNV. Electroencephalogr Clin Neurophysiol. 1993; 87(4):235–241. [PubMed: 7691554]

Rosahl SK, Knight RT. Role of prefrontal cortex in generation of the contingent negative variation. Cereb Cortex. 1995; 5(2):123–134. [PubMed: 7620289]

Rypma B, D'Esposito M. The roles of prefrontal brain regions in components of working memory: effects of memory load and individual differences. Proc Natl Acad Sci U S A. 1999; 96(11):6558–6563. [PubMed: 10339627]

Rypma B, D'Esposito M. A subsequent-memory effect in dorsolateral prefrontal cortex. Brain Res Cogn Brain Res. 2003; 16(2):162–166. [PubMed: 12668223]

Saalmann YB, Pigarev IN, Vidyasagar TR. Neural mechanisms of visual attention: how top-down feedback highlights relevant locations. Science. 2007; 316(5831):1612–1615. [PubMed: 17569863]

Scalaidhe SP, Wilson FA, Goldman-Rakic PS. Face-selective neurons during passive viewing and working memory performance of rhesus monkeys: evidence for intrinsic specialization of neuronal coding. Cereb Cortex. 1999; 9(5):459–475. [PubMed: 10450891]

Schall JD. Neural basis of deciding, choosing and acting. Nat Rev Neurosci. 2001; 2(1):33–42. [PubMed: 11253357]

Schmolesky MT, Wang Y, Hanes DP, Thompson KG, Leutgeb S, Schall JD, Leventhal AG. Signal timing across the macaque visual system. J Neurophysiol. 1998; 79(6):3272–3278. [PubMed: 9636126]

Shibata T, Nishijo H, Tamura R, Miyamoto K, Eifuku S, Endo S, Ono T. Generators of visual evoked potentials for faces and eyes in the human brain as determined by dipole localization. Brain Topography. 2002; 15:51–63. [PubMed: 12371677]

Sigman M, Jobert A, Lebihan D, Dehaene S. Parsing a sequence of brain activations at psychological times using fMRI. Neuroimage. 2007; 35(2):655–668. [PubMed: 17275341]

Srinivasan, H. High-Resolution EEG: Theory and Practice. Event-Related Potentials. In: Handy, TC., editor. A Methods Handbook. London: The MIT Press; 2005. p. 167-188.

Sun FT, Miller LM, D'Esposito M. Measuring temporal dynamics of functional networks using phase spectrum of fMRI data. Neuroimage. 2005; 28(1):227–237. [PubMed: 16019230]

Sun FT, Miller LM, Rao AA, D'Esposito M. Functional connectivity of cortical networks involved in bimanual motor sequence learning. Cereb Cortex. 2007; 17(5):1227–1234. [PubMed: 16855008]

Thompson KG, Bichot NP, Schall JD. Dissociation of visual discrimination from saccade programming in macaque frontal eye field. J Neurophysiol. 1997; 77(2):1046–1050. [PubMed: 9065870]

Tomita H, Ohbayashi M, Nakahara K, Hasegawa I, Miyashita Y. Top-down signal from prefrontal cortex in executive control of memory retrieval. Nature. 1999; 401(6754):699–703. [PubMed: 10537108]

Walter WG, Cooper R, Aldridge VJ, McCallum WC, Winter AL. Contingent Negative Variation: An Electric Sign Of Sensorimotor Association and Expectancy in the Human Brain. Nature. 1964; 203:380–384. [PubMed: 14197376]

Womelsdorf T, Schoffelen JM, Oostenveld R, Singer W, Desimone R, Engel AK, Fries P. Modulation of neuronal interactions through neuronal synchronization. Science. 2007; 316(5831):1609–1612. [PubMed: 17569862]

Yago E, Duarte A, Wong T, Barceló F, Knight RT. Temporal kinetics of prefrontal modulation of the extrastriate cortex during visual attention. Cogn Affect Behav Neurosci. 2004; 4(4):609–617. [PubMed: 15849901]

Zarahn E, Aguirre G, D'Esposito M. A trial-based experimental design for fMRI. Neuroimage. 1997; 6(2):122–138. [PubMed: 9299386]

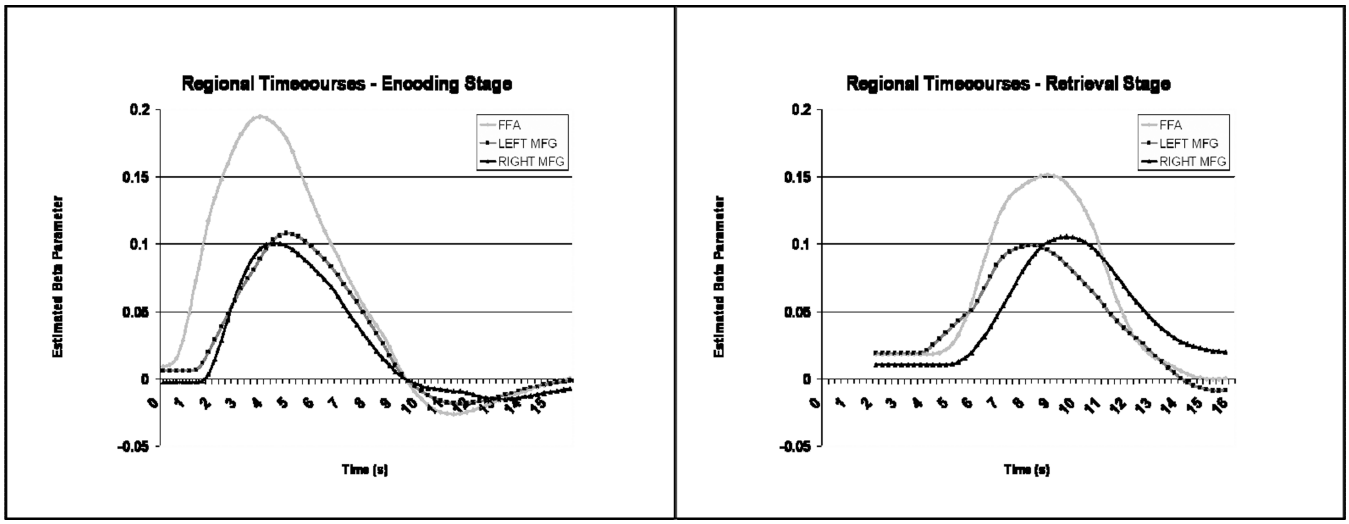

Figure 1.

– Regional timecourses for encoding (left panel) and retrieval (right panel) stages. AT encoding, onset and peak measures in bilateral MFG lag behind the temporal parameters of the FFA response. At retrieval, LMFG shows earlier peak responses than both FFA and rMFG – consistent with an early role of the PFC in retrieval processes.

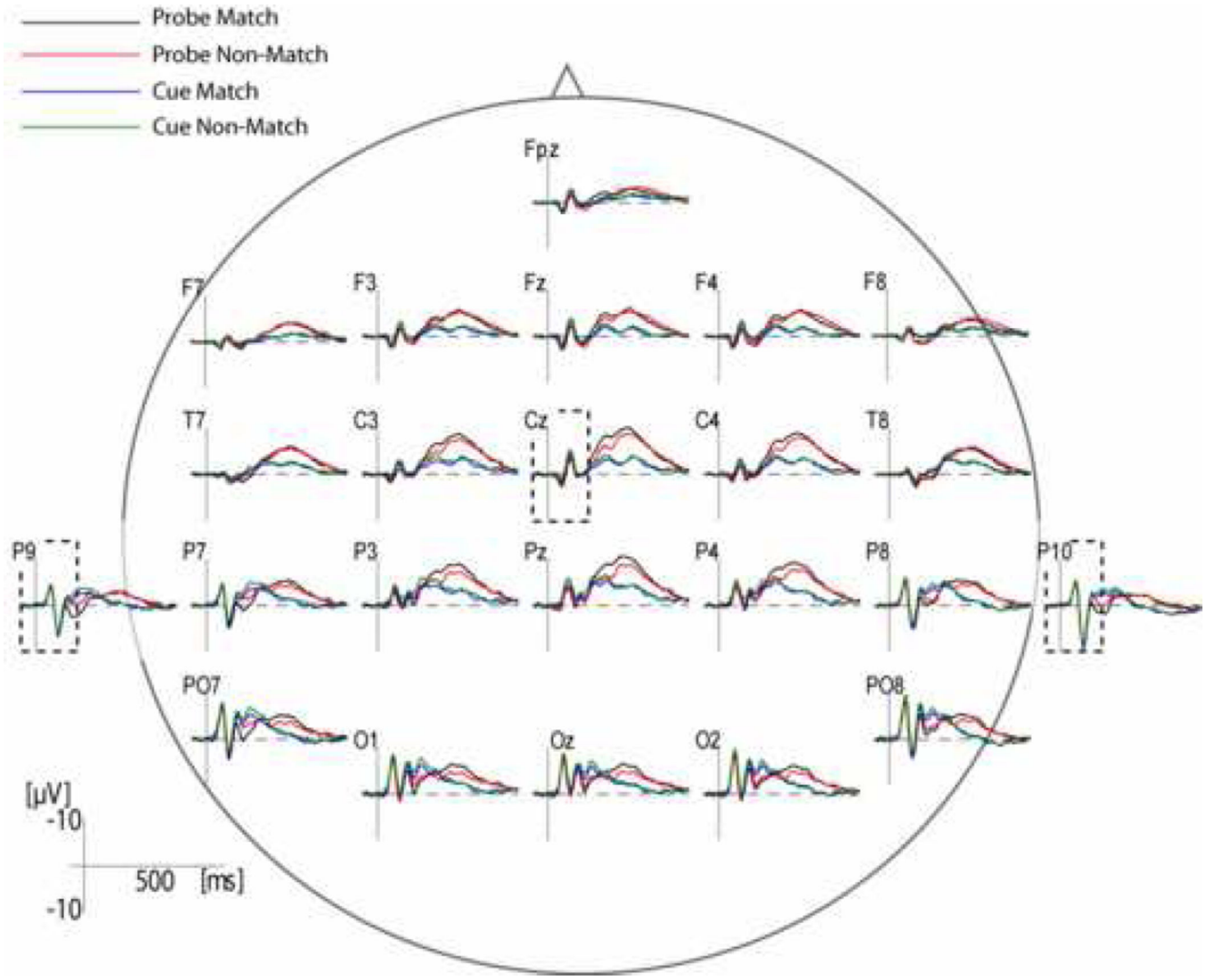

Figure 2.

ERPs to cue and probe stimuli in match and non-match conditions. Patterns across frontal and posterior electrodes reveal significant differences between cue and probe conditions.

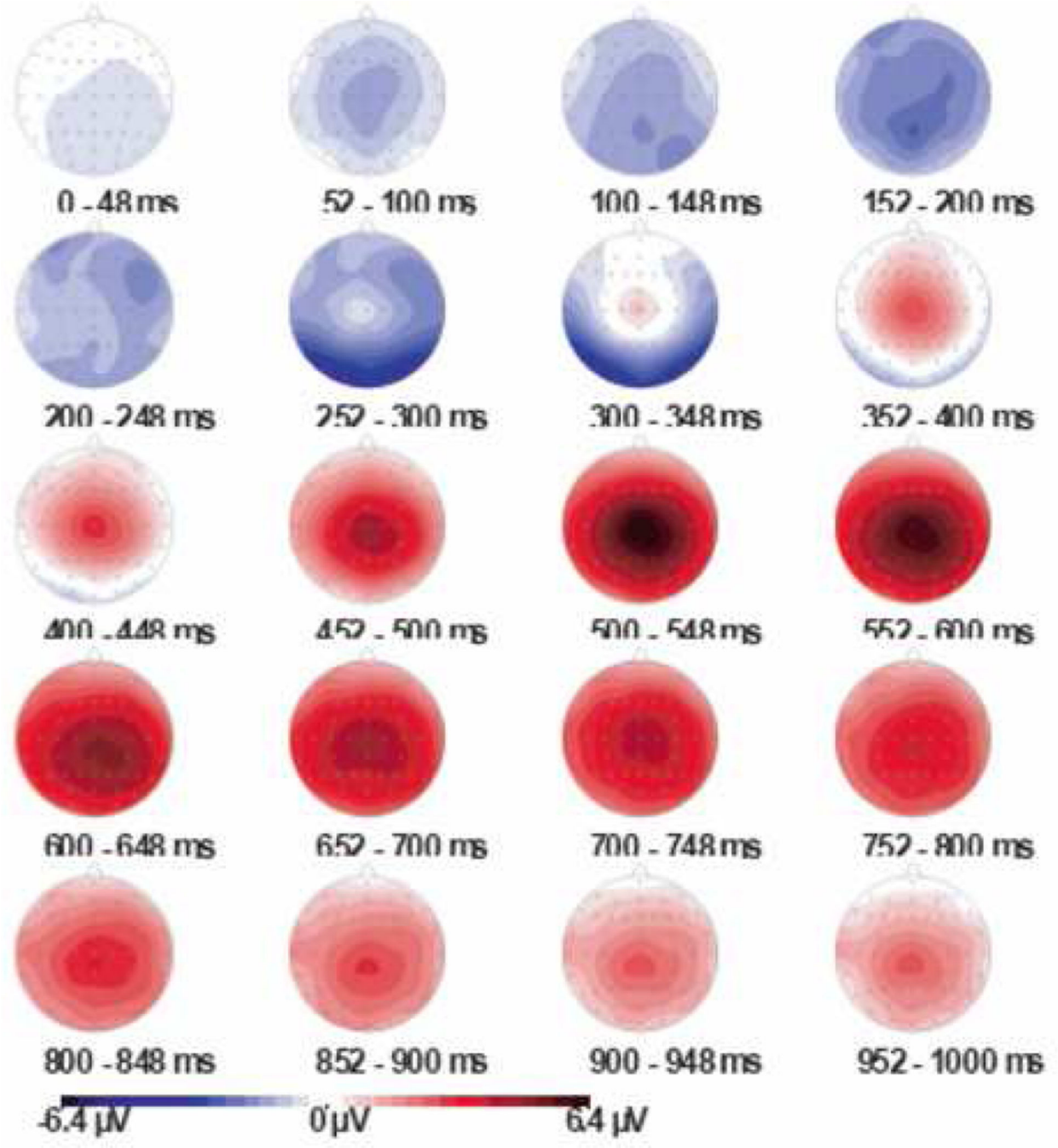

Figure 3.
Probe – Cue difference distributions

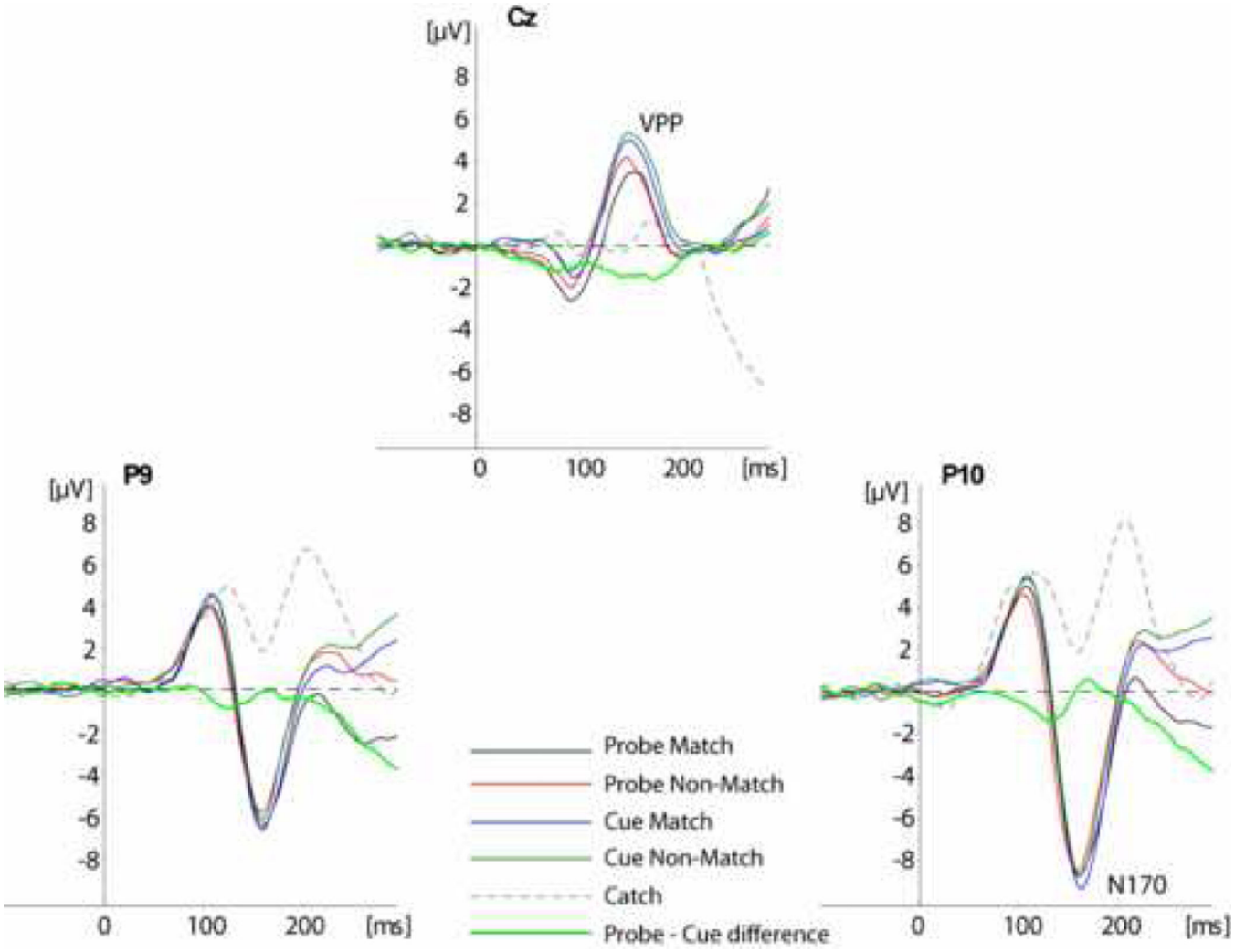

Figure 4.
Early ERP waveforms

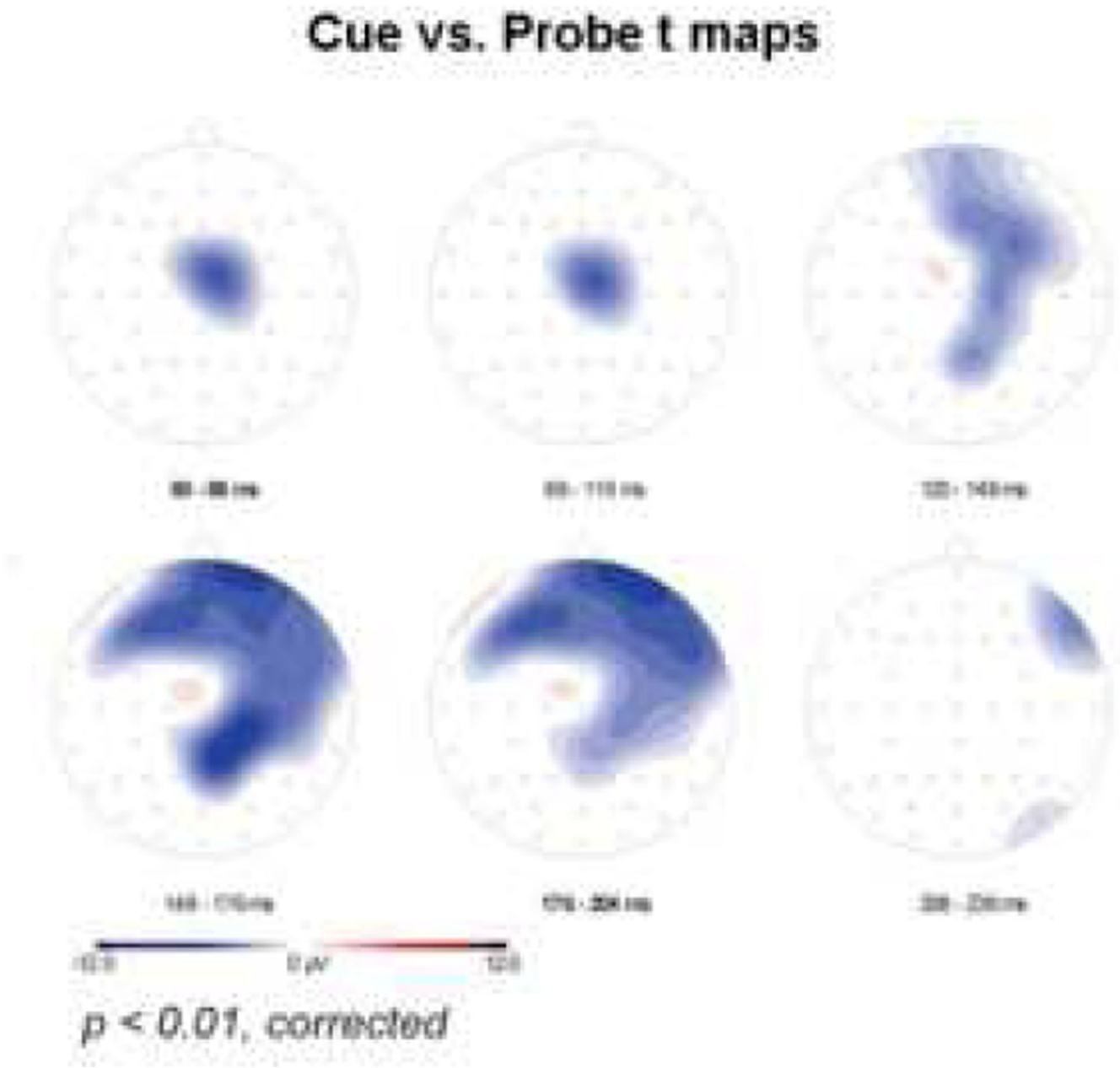

Figure 5.
Cue vs. Probe t Maps

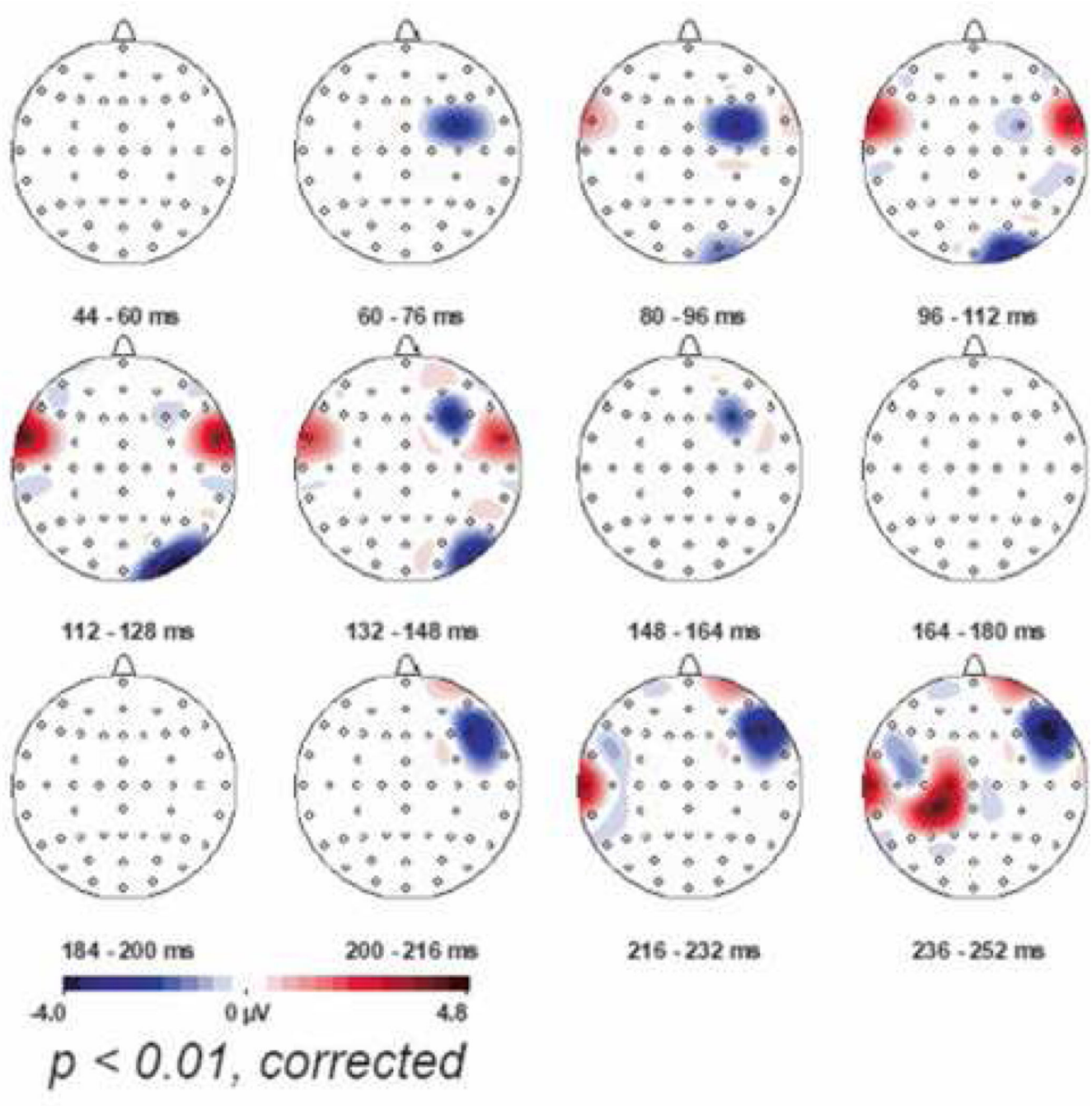

Figure 6.
Probe - Cue Difference, CSD maps

Table 1

Summary slide of mean latency values across regions and WM stages.

Stage	**Encoding (Cue stimulus)**		**Retrieval (Probe Stimulus)**	
Measure	***Onset***	***Peak***	***Onset***	***Peak***
FFA	1770ms	4747ms	2288ms	5612ms
LMFG	2940ms	5943ms	2564ms	5099ms
RMFG	2821ms	5833ms	3039ms	6500ms