Multimodal imaging of repetition priming: Using fMRI, MEG, and intracranial EEG to reveal spatiotemporal profiles of word processing

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Abstract

Repetition priming is a core feature of memory processing whose anatomical correlates remain poorly understood. In this study, we use advanced multimodal imaging (functional magnetic resonance imaging (fMRI) and magnetoencephalography; MEG) to investigate the spatiotemporal profile of repetition priming. We use intracranial electroencephalography (iEEG) to validate our fMRI/MEG measurements. Twelve controls completed a semantic judgment task with fMRI and MEG that included words presented once (new, ‘N’) and words that repeated (old, ‘O’). Six patients with epilepsy completed the same task during iEEG recordings. Blood-oxygen level dependent (BOLD) responses for N vs. O words were examined across the cortical surface and within regions of interest. MEG waveforms for N vs. O words were estimated using a noise-normalized minimum norm solution, and used to interpret the timecourse of fMRI. Spatial concordance was observed between fMRI and MEG repetition effects from 350 to 450 ms within bilateral occipitotemporal and medial temporal, left prefrontal, and left posterior temporal cortex. Additionally, MEG revealed widespread sources within left temporoparietal regions, whereas fMRI revealed bilateral reductions in occipitotemporal and left superior frontal, and increases in inferior parietal, precuneus, and dorsolateral prefrontal activity. BOLD suppression in left posterior temporal, left inferior prefrontal, and right occipitotemporal cortex correlated with MEG repetition-related reductions. iEEG responses from all three regions supported the timecourse of MEG and localization of fMRI. Furthermore, iEEG decreases to repeated words were associated with decreased gamma power in several regions, providing evidence that gamma oscillations are tightly coupled to cognitive phenomena and reflect regional activations seen in the BOLD signal.

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Introduction

Repetition priming has been studied extensively in cognitive neuroscience, but its exact neural correlates remain poorly understood. fMRI studies have demonstrated response suppression, the main neural correlate of priming, in a number of cortical regions following word repetitions. Reliable decreases in blood-oxygen level dependent (BOLD) responses are consistently reported in left ventral occipitotemporal, posterior temporal, and left inferior frontal cortex—regions implicated in word form identification (Allison et al., 1999), lexical access, and semantic processing (Marinkovic et al., 2003; Matsumoto et al., 2005). Repetition of words also has been associated with increased activity in bilateral precuneus, frontoparietal, and hippocampal cortex—regions implicated in resting state and episodic retrieval processes (Weiss et al., 2009). What is not clear from fMRI is precisely when repetition effects occur during the course of word processing.

Unlike fMRI, MEG provides a highly accurate picture of the temporal dynamics of cognitive processes, allowing one to visualize repetition effects in real time. MEG studies of priming have revealed reductions in the N400 response—an event-related field (ERF) implicated in semantic processing—to repeated words from ~350 to
450 ms following word presentation. MEG N400 reductions have been reported in previous studies in similar regions to those identified with fMRI (Marinkovic et al., 2003). In addition, MEG studies have generally revealed priming effects that are more widespread in temporoparietal regions, often extending into the anterior temporal pole—a region not always captured with fMRI due to signal loss (Devlin et al., 2000).

However, neuroimaging methods such as fMRI and MEG rely on noninvasively recorded responses, which cannot provide unequivocal evidence of local neuronal generators. In addition, it has been suggested that some discrepancies between fMRI and MEG patterns may stem from the fact that the BOLD signal is closely coupled with power changes in high gamma activity (Lachaux et al., 2007). Thus, discrepancies between fMRI and MEG patterns may stem from the fact that the BOLD signal is closely coupled with power changes in high gamma activity (Lachaux et al., 2007)—a frequency range not always detected at the scalp due to the low amplitude characteristic of gamma waveforms (Dalal et al., 2009), contamination with EMG artifact (Whitham et al., 2008) and microsaccades (Yuval-Greenberg et al., 2008). Increased gamma oscillations have been associated with a number of cognitive processes, including language and memory (Lachaux et al., 2007; Sederberg et al., 2007). Therefore, understanding their local generation may further enhance knowledge of word priming effects. Intracranial electroencephalography (iEEG) is the only current method capable of localizing such sources unambiguously and providing validation of the temporal, spatial, and spectral features of the fMRI and MEG repetition priming effects (Halgren, 2004b).

The goal of this study was to utilize sophisticated multimodal imaging to evaluate the spatiotemporal dynamics of repetition priming. We leveraged the high temporal resolution of MEG and iEEG to examine the time course of regional fMRI activations. In addition, we explored the regions and time windows during which the electromagnetic and hemodynamic priming effects showed the strongest correlation across participants. iEEG recordings were evaluated in regions that showed strong MEG and/or fMRI repetition effects, and the spatiotemporal and spectral features of iEEG responses were analyzed. We hypothesized that fMRI and MEG would show repetition priming effects in left inferior frontal, ventral occipitotemporal, and superior temporal cortex. We predicted that the regions associated with response suppression in fMRI would show strong correlations with reductions in MEG sources between ~350 and 450 ms—capturing peak N400 effects. We predicted that iEEG recordings would support previous studies demonstrating local generators of the N400 in multiple perisylvian regions (Halgren, 2004a), and that N400 iEEG responses would be particularly evident in the high gamma range.

Materials and methods

Participants

Twelve right-handed, healthy controls between the ages of 19 and 36 (six males) and six patients undergoing invasive inpatient monitoring at the New York University (NYU) Comprehensive Epilepsy Center for treatment of drug-resistant epilepsy participated in the study. The study was approved by the Institutional Review Board at NYU and each subject’s consent was obtained in accordance with the ethical standards promulgated in the Declaration of Helsinki. Handedness in all control participants was assessed with the Edinburgh Handedness Inventory (Oldfield, 1971). MEG and fMRI data were available for all healthy controls, whereas intracranial data only are provided for the patients. Table 1 provides clinical information for the six patients.

Semantic judgment task

All 12 healthy controls completed comparable versions of a semantic judgment task for both fMRI and MEG and all patients completed the same semantic judgment task during iEEG recordings. In this task, participants were instructed to respond by pressing a button in response to low-frequency target items (i.e., animals). Task stimuli were presented visually as white letters on a black background in Arial font. Stimuli consisted of 400 novel words that were presented only once, 400 “old” words (20 repetitions of 20 words), 400 consonant letter strings, 400 false font stimuli, and 80 target words (i.e., animals). In order to minimize expectancy effects, repeating words did not occur in the same order each time. All real word stimuli were 4–8 letter nouns, with a written lexical frequency of 3–80 per 10 million (Francis and Kucera, 1982). Data were collected using a rapid stimulus onset asynchrony (SOA; 600 ms) and a very large number of trials per condition in order to obtain electrophysiological data with a high signal-to-noise ratio (SNR) in a short time frame. For all three modalities, the experimental task was organized into two separate lists, each list taking approximately 10 min to complete. The tasks were programmed using Presentation software (Neurobehavioral Systems, Inc). The order of MEG and fMRI sessions was counterbalanced across healthy controls.

fMRI

A blocked version of the semantic judgment task was designed for fMRI in order to maximize the signal-to-noise ratio (SNR) in regions believed to be involved in lexical–semantic processing, but also known to be susceptible to signal loss (Devlin et al., 2000). Sixty blocks of stimuli were created that included 10 blocks of new words, repeating (old) words, and letter strings, and 30 blocks of false font stimuli (i.e., sensory controls). This design produced 30 active blocks and 30 control blocks. Each block contained 40 words of one stimulus type, plus two target words. Blocks of new words and consonant strings were presented in random order. Blocks of old words were not randomized. Rather, each old word was presented four times in each of the five blocks (i.e., 20 repetitions), and blocks were spaced such that old words only occurred approximately every 5–10 s per block and blocks of words repeated every 2–3 min. The button response was to low frequency targets (i.e., animals) in each block.

MEG and iEEG

Event-related versions of the semantic judgment task were designed for MEG and iEEG such that each of the old words was presented approximately every 30 s (±10 s) and there were on average 42 intervening stimuli between presentations of a given old word. Novel words, consonant strings, and false fonts were presented in random order throughout each list. However, the sequence of
smoothness of the data was estimated from normalized residuals. This runs for each contrast of interest (N: Jenkinson and Smith, 2001), and analyzed using FMRI Expert Analysis were co-registered to T1-weighted images (Jenkinson et al., 2002; pre-whitened using FILM (Woolrich et al., 2001). Functional scans filtered at sigma=50 s and ltered off-line at 40 Hz (transition band = 4 Hz), high-pass filtered at 0.2 Hz (transition band = 4 Hz), detrended, baseline corrected, and downsampled by a factor of 4 before separate averages were created for each subject. Epochs containing EOG amplitudes exceeding 280 μV in the EOG electrode or magnetometer amplitudes exceeding approximately 3000 IT were excluded from the averages. Grand averages for each stimulus type were created by averaging across the two runs.

**MEG source analysis**

To estimate the time courses of cortical activity, distributed source estimates were calculated from magnetometer data using dynamic statistical parametric mapping (dSPM) (Dale et al., 2000). This method is based on the assumption that the main generators of MEG and EEG signals are localized in the gray matter. Once the exact shape of the cortical surface is known, this information can be used to reduce the MEG solution space. Furthermore, normalization procedures are used that take into account the noise sensitivity at each spatial location, allowing for statistical parametric maps that provide information about the estimated signal at each location relative to the noise. First, the cortical surface was subsampled to about 2500 dipole sites in the fMRI data. In each case, a functional label was associated with the activity for each participant according to their condition. The method generates statistical maps that are square root of F distributed and represent the activity for each participant throughout the time course. These values were then averaged on the cortical surface across individuals after aligning their sulcal-gyral patterns (Dale and Halgren, 2001). From the mean group activity maps, thresholded t-stat maps were calculated that take into account within-group variability and the same cluster based-thresholding approach used for the fMRI analysis was performed on selected time frames for the MEG data (FWHM = 22 mm; t-statistics thresholded at p<0.001 and cortical surface clusters smaller than 257 mm² excluded; corrected cluster p<0.05). Three time windows were selected based on previous MEG (Dhond et al., 2001; Marinkovic et al., 2003) and intracranial (Halgren et al., 1994; Halgren et al., 2006) studies of semantic and repetition priming that have revealed the approximate time course associated with lexical access (~200–240 ms), semantic processing (~350–450 ms), and conscious recollection (~500–600 ms). The last time window was of interest because previous studies have demonstrated late repetition effects that occur ~540 ms.
even in the context of incidental memory tasks (Dale et al., 2000). Finally, ROI analyses were performed using the ROIs derived from the fMRI surface maps. By using identical surface-based ROIs, statistical maps (t-stats), and methods for surface-based clustering of the data, we sought to optimize comparisons between our MEG and fMRI results. MEG waveforms across the entire 0–600 ms timecourse were extracted from each of the surface-based ROIs.

iEEG acquisition

iEEG data were recorded from six patients undergoing invasive monitoring. Each patient was implanted with 96 to 208 clinical electrode contacts in the form of grid, strip and/or depth arrays. EEG activity was recorded from 1 to 130 Hz (3 dB down) using Nicolet clinical amplifier and digitized at 400 Hz, or from 0.6 to 1000 Hz and digitized at 2000 Hz using a custom NSpike recording system (see supplementary figure). Placement of electrodes was based entirely on clinical considerations for identification of seizure foci, as well as eloquent cortex during stimulation mapping. Consequently, a wide range of brain areas was covered, with coverage extending widely into non-epileptogenic regions. Electrode localization was computed by co-registering two T1-weighted MRIs, one obtained preoperatively and one on the day after implant surgery with the electrodes in place. A spatial optimization algorithm was used to integrate additional information from the known array geometry and intra-operative photos to achieve high spatial accuracy of the electrode locations in relation to the cortical MRI surface created during Freesurfer reconstruction.

iEEG analysis

iEEG was down-sampled to 400 Hz if necessary and epoched using 500 ms before and 1000 ms after each stimulus. Data were analyzed in Matlab using the Fieldtrip software package (http://www.ru.nl/fcdonders/fieldtrip/) and custom analysis and visualization routines. For ERP analysis, post-processing steps included a bandpass-filter at .1–30 Hz, detrending and baseline correction. Epochs containing artifacts were identified by visual inspection of bandpass filtered data and were excluded from further time- and frequency-domain analysis. Raw data were transformed from the time-domain to the time-frequency domain using the complex Morlet wavelet transform (Lachaux et al., 1999). Constant temporal and frequency resolution across target frequencies was obtained by adjusting the wavelet widths according to the target frequency. The wavelet widths increase linearly from 14 to 38 as frequency increases from 70 to 190 Hz, resulting in a constant temporal resolution (σ_t) of 16 ms and frequency resolution (σ_f) of 10 Hz. For each epoch, spectral power was calculated from the wavelet spectra, normalized by the inverse square frequency to adjust for the rapid drop-off in the power spectrum with frequency, and averaged from 70 to 190 Hz, excluding line noise harmonics. Visual inspection of the resulting high gamma power waveforms revealed additional artifacts not apparent in the time-domain signal, and the artifactual epochs were excluded from the gamma power analysis. Both ERP and gamma waveforms were compared across stimulus types using a nonparametric randomization test with temporal clustering to correct for multiple comparisons (Maris and Oostenveld, 2007).

Statistical analysis

Functional MRI t-stat cluster maps for the N–O and O–N contrasts were compared to the t-stat cluster maps generated for MEG of the N vs. O difference waveform at each of the three time windows of interest. To examine the time course of regional priming effects, time window × condition repeated measures (RM) ANOVAs were performed on the average source estimates within each ROI and hemisphere. To explore the relationship between the hemodynamic and electromagnetic repetition priming effects, Spearman correlations were performed between fMRI percent signal change and modulation of the MEG difference waveform within each ROI and time window. Percent signal change was selected due to evidence that this measure of the BOLD response correlates with N400 priming effects in EEG studies (Matsumoto et al., 2005).

Results

Fig. 1 displays cluster-based t-stat surface maps of the N–O (red-yellow) and O–N (blue-cyan) contrasts for fMRI (left panel) and the N vs. O difference waveform (red-yellow) for MEG time windows of
interest (right panel). Fig. 2 portrays the same fMRI cluster maps, with MEG timecourses extracted from significant ROIs identified on the fMRI surfaces.

**fMRI**

Prominent repetition-related effects for fMRI were observed within 16 regions in the left or right hemisphere. For the N→O contrast, significant clusters were observed in the left inferior prefrontal extending into the precentral gyrus, pars orbitalis, posterior superior temporal, middle temporal, parahippocampal, and superior medial frontal, as well as in bilateral entorhinal, lateral occipitotemporal, and ventral occipitotemporal cortex that extends into anterior fusiform on the left. In addition, O→N responses were observed within bilateral dorsolateral prefrontal cortex, precuneus, inferior parietal/supramarginal cortex. Average percent signal change for the N→O and O→N responses are provided for each ROI in Table 2.

**MEG**

Cluster-thresholded surface maps of the MEG O vs. N difference waveform revealed a dynamic pattern of activity that was observed primarily in bilateral orbital and ventral occipitotemporal cortex early on (~80–120 ms), followed by repetition effects from ~200 to 240 ms in the superior temporal cortex bilaterally, left dorsolateral prefrontal, inferior parietal, and left ventral occipitotemporal regions. Inspection of the waveforms in Fig. 2 reveals that this early activity is greater for O relative to N words across most regions and may reflect a temporal advantage for processing repeating word stimuli (Marinkovic et al., 2003). This pattern of activity appears increasingly left lateralized from 350 to 450 ms, and is characterized by greater responses to N relative to O words, consistent with modulation of the N400 response to repeated stimuli. In particular, prominent clusters of activity were observed within left inferior prefrontal, left superior, middle, and inferior temporal regions, left ventral occipitotemporal (lingual and fusiform), left temporal pole, left entorhinal, left parahippocampal, and left inferior parietal cortex including parts of the angular and supramarginal gyri. In addition, activity is observed within the right lateral and ventral occipitotemporal cortex (mostly lingual). By ~500–600 ms, activity is seen within many of the same regions and again appears more bilaterally distributed.

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Average percent signal change for each region of interest.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Region of interest</td>
<td>Mean % signal change (standard deviation)</td>
</tr>
<tr>
<td>N→O</td>
<td></td>
</tr>
<tr>
<td>Left entorhinal</td>
<td>.16 (.05)</td>
</tr>
<tr>
<td>Left ventral occipitotemporal</td>
<td>.14 (.04)</td>
</tr>
<tr>
<td>Left posterior inferior frontal</td>
<td>.16 (.04)</td>
</tr>
<tr>
<td>Left superior temporal</td>
<td>.15 (.03)</td>
</tr>
<tr>
<td>Left middle temporal</td>
<td>.15 (.04)</td>
</tr>
<tr>
<td>Left pars orbitalis</td>
<td>.14 (.04)</td>
</tr>
<tr>
<td>Left parahippocampal</td>
<td>.16 (.03)</td>
</tr>
<tr>
<td>Left lateral occipital</td>
<td>.16 (.04)</td>
</tr>
<tr>
<td>Left superior medial frontal</td>
<td>.19 (.02)</td>
</tr>
<tr>
<td>Right entorhinal</td>
<td>.13 (.03)</td>
</tr>
<tr>
<td>Right ventral occipitotemporal</td>
<td>.14 (.03)</td>
</tr>
<tr>
<td>Right lateral occipitotemporal</td>
<td>.14 (.03)</td>
</tr>
<tr>
<td>O→N</td>
<td></td>
</tr>
<tr>
<td>Left dorsolateral prefrontal</td>
<td>.15 (.03)</td>
</tr>
<tr>
<td>Left inferior parietal</td>
<td>.15 (.04)</td>
</tr>
<tr>
<td>Left precuneus</td>
<td>.14 (.04)</td>
</tr>
<tr>
<td>Right dorsolateral prefrontal</td>
<td>.14 (.04)</td>
</tr>
<tr>
<td>Right inferior parietal</td>
<td>.14 (.03)</td>
</tr>
<tr>
<td>Right precuneus</td>
<td>.13 (.03)</td>
</tr>
</tbody>
</table>
To estimate the time course within selected ROIs, time by condition RM ANOVAs were performed (see Fig. 2). Within the left hemisphere, time by condition interactions were observed within the ventral occipitotemporal \([F(2, 22) = 3.8, p < .05]\), superior temporal \([F(2, 22) = 3.7, p < .05]\), middle temporal \([F(2, 22) = 4.7, p < .05]\), pars orbitalis \([F(2, 22) = 3.8, p < .05]\), supramarginal \([F(2, 22) = 4.0, p < .05]\), inferior frontal \([F(2, 22) = 3.9, p < .05]\), entorhinal \([F(2, 22) = 4.1, p < .01]\), parahippocampal \([F(2, 22) = 3.5, p < .05]\), and temporal pole \([F(2, 22) = 3.8, p < .05]\). Within the right hemisphere, time by condition interactions were observed in the right ventral occipitotemporal only \([F(2, 22) = 3.4, p < .05]\). In each case, new words produced greater responses than old words, but only in the 350–450 ms time window. Despite a trend for O vs N word responses in the left and right dorsolateral prefrontal and superior temporal ROIs in the 500–600 ms time window and across many regions in the 200–240 ms time window (\(p\)-values between .05 and .10), none of the O-N comparisons reached statistical significance at the ROI level.

### fMRI/MEG correlational analysis

Visual inspection of the surface maps and ROI waveforms reveals that the fMRI N-O effect most closely resembles the MEG 350–450 ms time window, presumably representing modulation of the N400 effect. In order to examine the relationship between the electromagnetic N400 and hemodynamic priming effects, Spearman correlations were calculated across subjects for each ROI between fMRI percent signal change values and MEG difference waveform values within each time window. Correlational analysis revealed a positive relationship between fMRI N-O and MEG N vs. O responses in the left inferior prefrontal (\(r = -.72, p < .01\)), left superior temporal (\(r = -.54, p < .05\)) and right ventral occipitotemporal (\(r = -.56, p < .05\)) ROIs, but only within the 350–450 ms time window. Despite similar spatial patterns of activity between MEG and fMRI at the surface level in other ROIs and time windows, the magnitude of the BOLD signal change did not correlate with the modulation MEG waveforms in other regions across individual subjects.

### Intracranial validation of MEG/fMRI repetition effects

Inverse methods for source localization based on MEG and fMRI require unproven a priori assumptions. In contrast, it is possible to demonstrate local generation from intracranial recordings without ambiguities. Thus, we also sampled responses to N vs. O words from intracranial recordings obtained in six patients. Event-related potentials and high gamma frequency analyses were performed on all patient responses. Table 3 summarizes the number of patients showing locally generated iEEG repetition effects within the 350–450 and 500–600 ms time windows.

### Event-related potential analysis

Fig. 3 shows examples of localized ERPs from four patients based on iEEG recordings. Of our six patients, four had grid coverage of the left posterior superior temporal gyrus/sulcus. Two of the four patients showed a locally generated N-O response between 350 and 500 ms in the vicinity of the left posterior superior temporal region in or near Wernicke’s area (Patients A and E). One patient showed an O-N response in the same region that peaked at 600 ms following stimulus presentation (Patient D). Only three patients had grids covering the left inferior frontal region near pars opercularis. Two of the three patients demonstrated a N-O response that peaked between 400 and 500 ms following stimulus presentation (Patients B and D). Five of six patients had grid coverage of the left lateral occipitotemporal region, either on the left (\(N = 4\)) or right (\(N = 1\)). Two of the four with left coverage showed a N vs. O difference in lateral occipitotemporal cortex that peaked between 350 and 500 ms (Patients A and E). The patient with right coverage showed a similar ERP response in right lateral occipitotemporal cortex (Patient C). Five patients had at least partial coverage of the ventral occipitotemporal region (\(Left = 3\); \(Right = 2\)), with one showing N-O differences on the left (Patient A) between 350 and 400 ms and two patients showing a N-O response on the right (Patients C and F) between 400 and 600 ms in this region. Four patients had partial coverage of the left dorsolateral prefrontal cortex. Two of these patients had strips extending into superior medial frontal cortex on the left. Of the four with left dorsolateral prefrontal coverage, one demonstrated N-O responses between 350 and 450 ms (Patient E). The same patient also demonstrated O-N responses between 500 and 700 ms in left dorsolateral prefrontal cortex. One patient had right dorsolateral prefrontal coverage and demonstrated a N-O response between 500 and 600 ms (Patient F). In addition, one patient with coverage of the left superior medial frontal region showed a local N-O response between 350 and 450 ms (Patient A).

### Time course of high gamma (70–190 Hz) power

In addition to the ERP analysis, high gamma responses between 70 and 190 Hz were sampled in all six patients from the same electrode locations as the ERPs (see examples in Fig. 4). High gamma activity was selected to investigate whether or not gamma oscillations show stronger co-localization with fMRI repetition effects than ERPs in one or more regions, as well as to interpret the valence of our ERP responses. Statistical analysis revealed gamma power differences to N vs. O words in the left superior temporal region in two patients (Patients A and E). In one patient, increased gamma power was associated with N-O words that peaked at 400 ms (Patient A), whereas the other patient showed O-N increases in gamma that peaked at 500 ms (Patient D). In both cases, the gamma oscillations supported ERPs generated at or near the same electrode location. Three patients showed high gamma differences in lateral occipitotemporal cortex (Patients C, D, and E; two left and one right). Of these responses, N-O differences were seen in two patients that began ~300 ms following word presentation (Patients C and D). In the other patient, O-N gamma differences were observed later in the time course, peaking around 500 ms (Patient E). Three patients showed increased gamma in ventral occipitotemporal cortex (Patients A, C, and F; one left and two right). In all cases, increased gamma oscillations peaked between 400 and 500 ms and reflected N-O responses. Two patients showed increased gamma for N-O words in left dorsolateral prefrontal (Patients A and D) associated with the N400 responses in the ERP data. In addition, increased gamma for O-N words was observed in the left dorsolateral prefrontal cortex in

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**Table 3**

Neocortical regions showing repetition effects in MEG and iEEG ERP and high gamma responses.

<table>
<thead>
<tr>
<th>Region of interest</th>
<th>MEG 350–450</th>
<th>ERP 350–450</th>
<th>MEG 500–600</th>
<th>ERP 500–600</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Left</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dorsolateral prefrontal</td>
<td>1/4</td>
<td>2/4</td>
<td>1/4</td>
<td>3/4*</td>
</tr>
<tr>
<td>Inferior frontal</td>
<td>X</td>
<td>2/3</td>
<td>0/3</td>
<td>2/3</td>
</tr>
<tr>
<td>Lateral occipitotemporal</td>
<td>2/4</td>
<td>2/4</td>
<td>1/4</td>
<td>1/4*</td>
</tr>
<tr>
<td>Ventral occipitotemporal</td>
<td>X</td>
<td>2/4</td>
<td>2/4</td>
<td>0/4</td>
</tr>
<tr>
<td>Superior medial frontal</td>
<td>1/2</td>
<td>0/2</td>
<td>0/2</td>
<td>1/2*</td>
</tr>
<tr>
<td>Superior temporal</td>
<td>X</td>
<td>2/4</td>
<td>1/4</td>
<td>1/4</td>
</tr>
<tr>
<td><strong>Right</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dorsolateral prefrontal</td>
<td>0/1</td>
<td>0/1</td>
<td>1/1</td>
<td>0/1</td>
</tr>
<tr>
<td>Lateral occipitotemporal</td>
<td>X</td>
<td>1/1</td>
<td>1/1</td>
<td>0/4</td>
</tr>
<tr>
<td>Ventral occipitotemporal</td>
<td>X</td>
<td>2/2</td>
<td>2/2</td>
<td>2/2</td>
</tr>
</tbody>
</table>

*Reflects increases in gamma power to O vs. N words. All other responses in the 70+Hz analysis reflect increases to N vs. O gamma power. X reflects a lack of any significant effect. Fractions represent number of patients showing an effect over number of patients with grid coverage in the anatomical region.
Discussion

Using advanced multimodal imaging, we demonstrate spatial concordance between fMRI and MEG N400 priming effects within left inferior prefrontal extending into precentral, left posterior superior temporal, left medial temporal, right lateral occipitotemporal, and bilateral ventral occipitotemporal cortex, encompassing much of the lingual and fusiform cortex on the left. We also provide iEEG validation of our MEG/fMRI responses in key regions in multiple patients and reveal co-localization between increased gamma power in iEEG and the fMRI BOLD response. Table 4 summarizes regions of spatiotemporal concordance associated with repetition priming across all three modalities. As can be seen, these priming patterns were largely characterized by reduced responses to repeated words, suggesting facilitation of word processing that is measurable in the hemodynamic and electromagnetic signals.

Furthermore, fMRI revealed repetition enhancement in which repeated words produced greater responses relative to new words in bilateral dorsolateral prefrontal, precuneus, and inferior parietal/supramarginal cortex. Although the MEG ROI analysis indicated a late (~500–600 ms) trend for O→N effects within these ROIs that exceeded our cluster threshold in the surface maps, the condition contrasts did not reach significance at the ROI level. This may be due to our short trial length (i.e., 600 ms), which precluded a complete analysis of the late repetition effects that often persist until 700–800 ms (Dale et al., 2000). This late effect has been referred to as the LPC/P3b and may reflect conscious recollection of the repeated words. This has been described previously in incidental memory tasks with a
large number of repetitions (Dale et al., 2000), presumably because word repetitions become apparent to the participant. In addition, the MEG surface maps reveal significant O vs. N differences within left ventral occipitotemporal and bilateral superior temporal clusters between 200 and 240 ms that appear to reflect early, transient enhancements to repeated stimuli, as reported in previous MEG studies of visual word processing (Dhond et al., 2001; Marinkovic et al., 2003). Although these N vs. O effects were not significant in the ROI analysis during the early time window, inspection of the waveforms reveals a trend toward O>N responses across several ROIs. Evidence for O>N activity within these ROIs was not captured by fMRI and it has been suggested that the transient nature of the early O>N response is not robust enough to overcome the sustained N>O response that dominates the fMRI BOLD response in these same regions (Marinkovic et al., 2003).

Correlational analysis between our fMRI and MEG repetition priming effects across individuals revealed that fMRI BOLD suppression correlated with MEG priming effects from 350 to 450 ms, but only within the left inferior prefrontal, left superior temporal, and right occipitotemporal region. Repetition suppression within each of these regions has been reported in previous neuroimaging studies of word and object priming (Marinkovic et al., 2003; Schacter and Buckner, 1998). Our within-subject, multimodal fMRI/MEG analysis provides further evidence that these regional priming effects are robust across imaging modalities. Although the relationship between electromagnetic and hemodynamic response changes is complex, a
The absence of an effect in the iEEG column does not necessarily represent discordance, interictal activity was detected.

Tomical substrates. Whereas early response suppression within involves multiple component processes with partially unique ana-

process. Rather, there is convincing evidence that repetition priming from iEEG of their local generation.

regions implicated in the N400 effect and by providing validation temporal gyrus (Matsumoto et al., 2005). We extend the literature by

support from iEEG recordings. However, there are several limitations during semantic memory retrieval (Gold and Buckner, 2002).

Investigation of the iEEG waveforms provides evidence of locally generated N400 responses within the left posterior superior temporal and left inferior prefrontal cortex (i.e., in or near Wernicke’s and Broca’s areas) that support our fMRI and MEG N400 reductions and represent core anatomical substrates of conceptual priming.

Taken together, our data provide evidence that the main repetition priming effects seen in fMRI BOLD responses are those associated with the MEG N400 reductions, and not necessarily with the more transient early or late repetition effects that are apparent in the MEG waveforms. This is consistent with previous findings that iEEG/MEG and BOLD responses correlate reasonably well for the N400, but not as strongly with the scalp P3b/LPC (Halgren, 2004b). However, our iEEG data did reveal O-N late repetition effects in left dorsolateral prefrontal cortex in all four patients with recordings sampled from this region that peaked between 500 and 600 ms and may reflect LPC/P3b effects. In three patients, the responses were observed in iEEG high gamma responses but not in the ERPs, suggesting that the BOLD effect associated with conscious recollection may be tightly coupled to increased power in the high frequency ranges not always captured with MEG or ERP measurements (Jerbi et al., 2009; Yuval-Greenberg et al., 2008).

The exact relationship between the BOLD response and increased gamma oscillations observed in cognitive tasks in not entirely known, but memory formation has been associated with increased gamma oscillations recorded with iEEG in left temporal and prefrontal regions (Sederberg et al., 2007). We extend the literature by demonstrating an association between increased gamma power and word priming effects in the context of an incidental memory task. Furthermore, we report increased gamma power for N-O responses in numerous patients in ventral and lateral occipitotemporal, inferior prefrontal, superior temporal, and medial prefrontal cortex that are also reflected in our fMRI activations many of which were not observed in the ERP data. These findings are consistent with an emerging literature demonstrating that gamma power co-localize with BOLD variations across numerous cortical regions during lexical-semantic tasks (Lachaux et al., 2007), presumably due to its correlation with local neuronal firing (Manning et al., 2009).

In this study, we provide multimodality evidence for the spatio-temporal profile of repetition word priming using fMRI/MEG with support from iEEG recordings. However, there are several limitations to our study that should be noted. First, whereas our MEG and iEEG tasks were event-related, we used a blocked version of the same task for fMRI. A blocked design was selected in order to increase the SNR, optimizing our ability to detect very subtle BOLD changes associated with repetition priming in anterior and ventral temporal lobe regions that are known to be susceptible to signal loss (Chee et al., 2003; Dale et al., 2000). Although numerous studies have reported highly similar patterns of activations between blocked and event-related fMRI designs using lexical-semantic tasks (Chee et al., 2003; Pilgrim et al., 2002; Wagner et al., 2005; Weiss et al., 2009), blocked presentation of items may induce strategies or lead to greater levels of habituation in some regions relative to event-related designs. This may explain the

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### Table 4
Neocortical regions showing significant repetition effects in each modality.

<table>
<thead>
<tr>
<th>Region of interest</th>
<th>fMRI</th>
<th>MEG 350–450 ms</th>
<th>iEEG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Temporal pole</td>
<td>X</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Dorsolateral prefrontal</td>
<td>X</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Entorhinal</td>
<td>X</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Inferior frontal*</td>
<td>X</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Lateral occipitotemporal</td>
<td>X</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Ventral occipitotemporal</td>
<td>X</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Middle temporal</td>
<td>X</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Parahippocampal</td>
<td>X</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Pars orbitalis</td>
<td>X</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Supramarginal</td>
<td>X</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Superior medial frontal</td>
<td>X</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Superior temporal</td>
<td>X</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Temporoparietal</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dorsolateral prefrontal</td>
<td>X</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Entorhinal</td>
<td>X</td>
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<td>Lateral occipitotemporal</td>
<td>X</td>
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<td>Ventral occipitotemporal</td>
<td>X</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Supramarginal</td>
<td>X</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Regions in which one or more patients showed a significant iEEG repetition effect. The absence of an effect in the iEEG column does not necessarily represent discordance, but may reflect inadequate grid coverage or the elimination of electrodes in which interictal activity was detected.

* Regions showing O-N effects. All other regions represent those showing N-O effects.

* Bolded regions are those demonstrating concordance across all three modalities.

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Recent neuroimaging research has demonstrated that repetition suppression across neocortical regions is unlikely to reflect a unitary process. Rather, there is convincing evidence that repetition priming involves multiple component processes with partially unique anatomical substrates. Whereas early response suppression within bilateral occipitotemporal regions likely reflects a “sharpening” of neural activity in response to the perceptual attributes of the stimulus (Fiebach et al., 2005; Schacter and Buckner, 1998) and visual word form priming (Cohen et al., 2002), the late effects (>300 ms) identified in our MEG responses suggest significant top-down influences that may reflect general attention-dependent priming for conceptual information (Klaver et al., 2007). This top-down interpretation is supported by iEEG ERP and/or high gamma recordings in five of six patients who showed late N-O responses in left or right occipitotemporal cortex in or near regions showing strong activation in fMRI and MEG. This late N-O effect in occipitotemporal cortex has not been previously reported across all three modalities and provides evidence that priming effects within extrastriate cortex are influenced by both feedforward and feedback mechanisms.

In addition, response suppression within left posterior temporal cortex has been attributed to facilitation of lexical access (Matsumoto et al., 2005) or encoding of a written word into a lexical representation (Klaver et al., 2007). This component of repetition priming appears to be independent of the earlier perceptual effects, and may represent automatic, spreading activation of a word’s representation. Our data demonstrate response suppression within left temporal cortex in fMRI and in the MEG waveforms that is highly lateralized and sustained after ~250 ms. This time period is congruent with other studies that have identified a lexical-processing stage that may represent a transitional stage between perceptual and conceptual priming (Marinkovic et al., 2003). However, the sustained effects observed in these regions in the MEG surface maps and waveforms indicate that left temporal regions also contribute to the main N400 component of repetition priming.

Response suppression within the left inferior prefrontal region is generally believed to reflect conceptual priming, including a reduced demand for semantic memory retrieval (Wagner et al., 2001) and/or facilitation of response selection (Thompson-Schill et al., 1997). Our MEG and fMRI data show response suppression in the left inferior frontal cortex that appears to evolve somewhat later than the priming effects observed in posterior temporal cortex and is maximal between 350 and 450 ms (i.e., peak N400 effect). The sustained response suppression in left temporal regions during this time supports the notion that left lateral temporal cortex is important for initial lexical access, as well as interactions with prefrontal regions during semantic memory retrieval (Gold and Buckner, 2002).

The exact relationship between the BOLD response and increased gamma oscillations observed in cognitive tasks in not entirely known, but memory formation has been associated with increased gamma oscillations recorded with iEEG in left temporal and prefrontal regions (Sederberg et al., 2007). We extend the literature by demonstrating an association between increased gamma power and word priming effects in the context of an incidental memory task. Furthermore, we report increased gamma power for N-O responses in numerous patients in ventral and lateral occipitotemporal, inferior prefrontal, superior temporal, and medial prefrontal cortex that are also reflected in our fMRI activations many of which were not observed in the ERP data. These findings are consistent with an emerging literature demonstrating that gamma power co-localize with BOLD variations across numerous cortical regions during lexical-semantic tasks (Lachaux et al., 2007), presumably due to its correlation with local neuronal firing (Manning et al., 2009).

In this study, we provide multimodality evidence for the spatio-temporal profile of repetition word priming using fMRI/MEG with support from iEEG recordings. However, there are several limitations to our study that should be noted. First, whereas our MEG and iEEG tasks were event-related, we used a blocked version of the same task for fMRI. A blocked design was selected in order to increase the SNR, optimizing our ability to detect very subtle BOLD changes associated with repetition priming in anterior and ventral temporal lobe regions that are known to be susceptible to signal loss (Chee et al., 2003; Dale et al., 2000). Although numerous studies have reported highly similar patterns of activations between blocked and event-related fMRI designs using lexical-semantic tasks (Chee et al., 2003; Pilgrim et al., 2002; Wagner et al., 2005; Weiss et al., 2009), blocked presentation of items may induce strategies or lead to greater levels of habituation in some regions relative to event-related designs. This may explain the
bilateral precuneus and lateral occipitotemporal activations seen in our fMRI data that were not apparent with MEG. Greater BOLD responses to repeated stimuli have been reported previously in bilateral precuneus (Horner and Henson, 2008) – a region implicated in episodic retrieval (Wagner et al., 2005) and task difficulty/workload (Korsnes et al., 2008; Scheibe et al., 2006). It is unclear in our study whether the fMRI responses observed in this region reflect conscious recollection of previous items or the lower task demands introduced by our blocked presentation. However, the presence of lateral occipitotemporal repetition effects in our iEEG recordings that co-localize with the fMRI activations suggest that task design differences are unlikely to account for the occipitotemporal findings. Although using identical task designs for fMRI and MEG/iEEG would appear ideal, there are possible limitations to this approach as well. Had we implemented an event-related fMRI design, we may have reduced our SNR and failed to detect subtle task effects in the anteriomedial temporal lobe that appear to be involved in repetition priming. Alternatively, we could have designed an event-related fMRI design with a higher number of trials per condition to increase the SNR. However, this would have resulted in a greater number of repetitions in our fMRI task relative to MEG and iEEG tasks. The number of repetitions has been shown to influence priming effects (Ostergaard, 1998), introducing another confound. Despite task differences, the high spatial correlation across imaging modalities in many critical regions suggests that most of the repetition priming effects were robust to differences in the task design.

Second, we used a very brief SOA (i.e., 600 ms) in order to increase our SNR by allowing for a large number of averages across task conditions in a relatively short time. This brief SOA diminished our ability to fully evaluate late MEG repetition effects that generally peak around 600 to 700 ms post-stimulus. Finally, it is important to note that iEEG data are acquired from patients who are undergoing evaluation for surgical resection of an epileptic focus. Therefore, many of the iEEG discharges were recorded. However, it is still possible that one or more patients that supported the temporal and spatial patterns detected with our non-invasive measures. Multimodal imaging data such as these provide unique insight into the timing, location, and spectral features of cognitive processes, such as repetition priming, and demonstrate the validity of using non-invasive measures for understanding complex brain functions.

Acknowledgments

The work was supported by National Institutes of Health (NIH) Grant K23NS056091 (C.R.M) and NS18741 (E.H.).

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.neuroimage.2010.06.069.

References


