

Aberrant Frontoparietal Function during Recognition Memory in Schizophrenia: A Multimodal Neuroimaging Investigation

Anthony P. Weiss,^{1,2} Cameron B. Ellis,^{1,2} Joshua L. Roffman,^{1,2} Steven Stufflebeam,² Matti S. Hamalainen,² Margaret Duff,^{1,2} Donald C. Goff,^{1*} and Daniel L. Schacter^{3*}

¹Department of Psychiatry, Massachusetts General Hospital, Boston, Massachusetts 02114, ²Athinoula A. Martinos Center for Biomedical Imaging, Charlestown, Massachusetts 02129, and ³Department of Psychology, Harvard University, Cambridge, Massachusetts 02138

Prefrontal–parietal networks are essential to many cognitive processes, including the ability to differentiate new from previously presented items. As patients with schizophrenia exhibit structural abnormalities in these areas along with well documented decrements in recognition memory, we hypothesized that these patients would demonstrate memory-related abnormalities in prefrontal and parietal physiology as measured by both functional magnetic resonance imaging and magnetoencephalography (MEG). Medicated outpatients with schizophrenia ($n = 18$) and age-matched healthy control subjects ($n = 18$) performed an old–new recognition memory task while physiological data were obtained. Whereas controls exhibited strong, bilateral activation of prefrontal and posterior parietal regions during successful identification of old versus new items, patients exhibited greatly attenuated activation of the right prefrontal and parietal cortices. However, within the patient group, there was strong correlation between memory performance and activation of these right-sided regions as well as a tight correlation between old–new effect-related activations in frontal and parietal regions, a pattern not seen in control subjects. Using MEG, control subjects— but not patients— exhibited a sequential pattern of old > new activity in the left posterior parietal cortex and then right prefrontal cortex; however, patients uniquely exhibited old > new activity in right temporal cortex. Collectively, these findings point to markedly different distributions of regional specialization necessary to complete the old–new item recognition task in patients versus controls. Inefficient utilization of prefrontal–parietal networks, with compensatory activation in temporal regions, may thus contribute to deficient old–new item recognition in schizophrenia.

Introduction

Patients with schizophrenia exhibit deficits in memory that limit their functional capacity within the community (Green, 2006) and interfere with their ability to adhere to treatment (Jeste et al., 2003; Heinrichs et al., 2008). These deficits are present from the earliest stages of the illness and cannot be fully explained as a side effect of pharmacotherapy (Simon et al., 2007). As currently available treatments have relatively little effect on these cognitive deficits (Keefe et al., 2007), identifying their underlying neural causes remains an important area for scientific inquiry.

The importance of the prefrontal cortex in normal human memory, and its potential role in the memory deficits seen in patients with schizophrenia, have been well described (Barbas and Zikopoulos, 2007; Ragland et al., 2007; Tan et al., 2007b;

Ranganath et al., 2008). Recent evidence has also highlighted an important contributory role of the parietal cortices in normal declarative memory processes (Wagner et al., 2005; Cabeza et al., 2008). This is not necessarily surprising; as the principal posterior heteromodal cortex, the parietal lobes represent a critical information crossroad, bringing together information experienced through diverse sensory streams. The importance of the parietal lobe in the pathophysiology of schizophrenia is also being increasingly recognized, with at least 10 studies demonstrating structural abnormalities specifically within the inferior parietal lobule (for review, see Torrey, 2007). Despite these findings, there has been as yet relatively little research on the functional role of this region in memory processing in patients with schizophrenia.

The connection between parietal and prefrontal cortices is thought to be particularly important and forms the basis for network-based models of human cognitive function (including episodic memory) (Fuster, 2006). The relevance of prefrontal and parietal activation to episodic memory have been robustly demonstrated in neurophysiology studies of the so-called “old–new effect” (Rugg and Curran, 2007), in which successful recognition of previously experienced items (relative to novel items) produces both characteristic event-related potentials (ERPs) in the posterior parietal and prefrontal cortices, as well as blood oxygenation level-dependent (BOLD) activation in the same regions (Wagner et al., 2005). We recently described significant perfor-

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*D.C.G. and D.L.S. contributed equally to this work.

Correspondence should be addressed to Dr. Anthony P. Weiss, Department of Psychiatry, Massachusetts General Hospital, 1 Bowdoin Square, Boston, MA 02114. E-mail: aweiss@partners.org.

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mance deficits in schizophrenia patients during an old–new item recognition paradigm (Weiss et al., 2008). The current experiment sought to assess prefrontal and parietal physiology during the old–new task in the same group of patients and controls in light of these performance differences.

Prefrontal and parietal physiology was assessed using two complementary methods: functional magnetic resonance imaging (fMRI) and magnetoencephalography (MEG). The use of MEG allowed us to obtain a better “real-time” measure of the temporal activity within these regions, as well as complementing a blood-flow based analysis with one based directly on electromagnetic activity change. Based on the extant literature, we hypothesized that both the parietal and frontal components of this old–new effect would be diminished in patients with schizophrenia. This work was presented in part at the International Congress on Schizophrenia Research, 2007 and 2009 (Weiss et al., 2007; Roffman et al., 2009).

Materials and Methods

Subjects. The demographic characteristics of the enrolled subjects and a detailed description of the memory paradigm have been previously reported (Weiss et al., 2008) and will be briefly summarized below. Before enrollment of subjects, the protocol was approved by the institutional review boards of Partners HealthCare and the Commonwealth of Massachusetts Department of Mental Health. All participants provided written informed consent after a complete description of the study and administration of a brief questionnaire to ensure capacity to consent.

Eighteen outpatients (12 males and 6 females) with *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (DSM-IV)-defined schizophrenia based on SCID (Structured Clinical Interview for DSM-IV Axis I Disorders) criteria (First et al., 1995) and 18 age-matched control subjects (11 males and 7 females) participated in the study. Patients had a mean duration of illness of 15.6 ± 11.4 years, and all but one were taking a stable dose of antipsychotic medication (14 on second-generation antipsychotics, two on conventional antipsychotics, one on a combination of second-generation and conventional, and one unmedicated). Patients predominantly exhibited negative symptoms [mean Scale for the Assessment of Positive Symptoms (SAPS) (Andreasen, 1984) score, 16.2 ± 16.0 ; Scale for the Assessment of Negative Symptoms (SANS) (Andreasen, 1983) score, 34.9 ± 21.0]. Control subjects were free of any axis I psychiatric condition and were not taking psychotropic medication. Neither patients nor control subjects had a history of major medical or neurological illness. No subject met DSM-IV criteria for alcohol or other substance use disorder (excepting nicotine dependence) within the past 3 months.

As described previously (Weiss et al., 2008), there were no significant between-group differences in age, parental socioeconomic status, or parental education. When compared with the patients with schizophrenia, control subjects had a higher level of attained formal education, better socioeconomic status, and higher overall verbal IQ as estimated by the North American Adult Reading Test (Blair and Spreen, 1989).

Old–new item recognition task. The experimental paradigm was adapted from a previously published source monitoring experiment (Wilding, 1999). Briefly, this recognition memory task comprised six alternating encoding and testing sessions conducted while subjects were positioned in the magnetic resonance imaging (MRI) and MEG scanners.

For fMRI scans, during each encoding session, participants saw and heard 26 consecutive words (13 spoken by a male; 13 spoken by a female) and identified the gender of the recorded voice using a keypad button. Words were rear-projected for 3000 ms onto a hemispherical tangent screen and viewed through a mirror mounted on the head coil of the magnetic resonance (MR) scanner. Each word was simultaneously presented aurally via pneumatic headphones at a clearly audible level using Presentation, version 0.80 (Neurobehavioral Systems). Immediately after this encoding session, participants were presented with 52 consecutive words (26 previously studied and 26 new) and were asked to identify

Table 1. Episodic memory performance under fMRI and MEG scanning conditions in patients and controls

	Controls (%)	Patients (%)	Statistics
fMRI			
Corrected recognition rate	70.4 ± 19.9	55.4 ± 22.5	$t = 2.12$, $df = 34$, $p < 0.05$
Source accuracy	77.5 ± 14.1	73.3 ± 16.0	$t = 0.83$, $df = 34$, $p = 0.41$
MEG			
Corrected recognition rate	74.1 ± 19.0	49.4 ± 23.5	$t = 3.43$, $df = 29$, $p < 0.005$
Source accuracy	79.3 ± 14.0	72.2 ± 11.9	$t = 1.70$, $df = 29$, $p = 0.10$

Patients made significantly more errors differentiating new from previously presented items than did controls (as indicated by the corrected recognition rate, which corresponds to hit rate minus false alarm rate). However, there were no between-group differences in the source accuracy of items that were deemed to be old (i.e., correctly recalling that the word was originally presented in a male vs female voice).

the original source of the voice (i.e., male, female, or new). Words were presented one at a time visually for 3000 ms (plus a 500 ms interstimulus interval), with subjects indicating their response (male, female, or new) by pressing one of three buttons on a keypad.

For MEG scans, a nearly identical procedure was used, with the following modifications: (1) a counterbalancing scheme was developed such that the words used for the two visits (fMRI and MEG) were completely nonoverlapping; and (2) a series of 2 s “blink trials” were interposed into both the encoding and retrieval aspects of the MEG version of the paradigm. Subjects were encouraged to blink only during these trials, which occurred every 15.5 s and were later removed during routine preprocessing of the data. During encoding, visual stimuli were back-projected at eye level for 3000 ms onto a screen located 36 inches in front of the subject, and concurrently presented auditory stimuli were presented via pneumatic headphones as described above. The order of scans (i.e., having MEG vs fMRI first) was counterbalanced across subjects. The median time between the two scans was 15 d in both patients and controls.

Task performance analysis. Statistical analysis of the behavioral data was performed using SPSS, version 11.0 (SPSS). Standard measures of old–new recognition memory and source memory performance were calculated, with group means for these variables compared using an unpaired Student *t* test. The corrected recognition rate (also sometimes called *Pr*) is a standard measure of recognition memory accuracy. It is similar to the *d'* statistic from signal detection theory in that it attempts to control for response bias by including both “hits” and “false alarms.”

MRI acquisition. Magnetic resonance imaging data were acquired with a 1.5 tesla Siemens Avanto whole-body clinical scanner (Siemens Medical Systems). After automated localizer, scout, and shimming procedures, a T1-weighted structural image with the same slice parameters as the functional images was obtained to aid in registration of functional to structural images. Functional images were then collected using a standard echoplanar imaging sequence [repetition time (TR), 2500 ms; echo time (TE), 40 ms; flip, 90°; voxel size, $3.1 \times 3.1 \times 5$ mm]. Thirty interleaved oblique coronal slices (5 mm width with 1 mm gap), oriented perpendicular to the anterior commissure–posterior commissure line, were obtained during each TR. In each of the six encoding runs, 37 images were collected (103 s scan duration), and in each of the six test runs 73 images were collected (193 s scan duration). After the functional runs were completed, two high-resolution structural scans were acquired using a three-dimensional magnetization-prepared rapid-acquisition gradient echo (MPRAGE) sequence (TR, 2730 ms; TE, 3.31 ms; flip, 7°; voxel size, $1.3 \times 1 \times 1.3$ mm).

MRI analysis. The functional MRI data were analyzed using the FreeSurfer Functional Analysis Stream (FS-FAST) (<http://surfer.nmr.mgh.harvard.edu/>) (Dale et al., 1999; Fischl et al., 1999a,b). For each subject, functional scans were motion corrected (Cox, 1996), spatially smoothed (using a 6 mm full width at half-maximum Gaussian kernel), and intensity normalized. Based on visual inspection of the data, we found that distortions, ghosting, and other artifacts were present when the signal-to-noise ratio (SNR) of the image was <300 . This value was therefore used as a standard cutoff, with all runs with an SNR of <300 discarded from additional analyses. This led to the removal of 16 of 108 retrieval runs (14.8%) from the control group and 25 of 105 retrieval runs (23.8%)

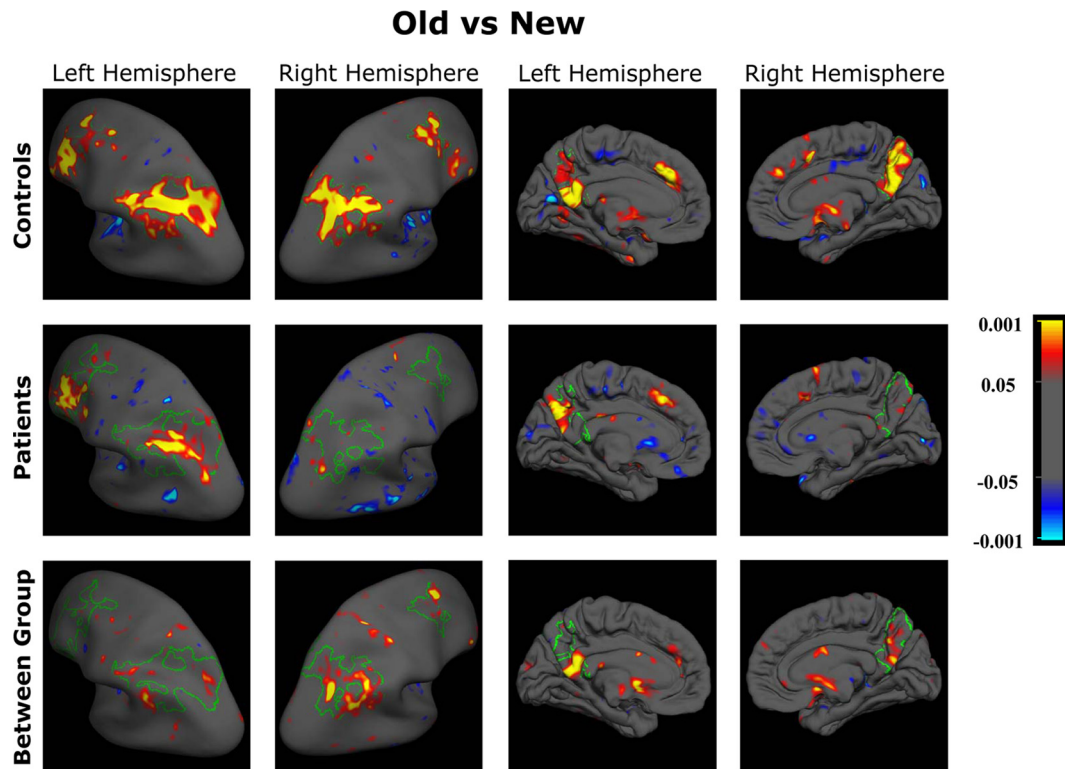


Figure 1. Statistical significance maps showing within- and between-group activation differences on the lateral (left side of figure) and medial (right side of figure) surface of the cortex. The “old versus new” contrast shows the activation differences between correctly recognized old items (regardless of source accuracy) and correctly rejected new items. Statistical significance is illustrated by color intensity, which represents an uncorrected vertex-level p value. Significant clusters (based on cluster-level thresholding) within the control old–new contrast are outlined in green; these regions were used as functional regions of interest in subsequent analyses.

from the schizophrenia group. The data from remaining runs had a high mean SNR in each group (control, 621 ± 218 ; schizophrenia, 732 ± 233 ; between-group unpaired t test, $t = 1.48$, $df = 32$, $p = 0.15$). To further evaluate whether differences in head motion could have contributed to between-group differences, we examined the mean motion vector (MMV) per TR in patients and controls. There was no difference between groups (control MMV, 0.042 mm/TR; patient MMV, 0.055 mm/TR; $t = -1.29$, $df = 32$, $p = 0.21$).

Based on the item type and subject response, five event types were identified: accurate source recollection of an old item [source hit (SH)], inaccurate source recollection of an old item [source miss (SM)], no recollection of an old item [miss (M)], accurate rejection of a new item [correct rejection (CR)], and falsely labeling a new item as previously presented [false alarm (FA)]. The time window used for event estimation was composed of a multiple of the TR, extending from 5 s prestimulus to 40 s after stimulus. The data were detrended using a second-order polynomial to remove low-frequency scanner drift. Temporal correlations of the noise were estimated and corrected using a prewhitening function that takes the global residual noise into account.

Functional and anatomical volumes were aligned by registering the anatomical volumes to a T1 template, registering the first image of the first functional run to a T2* template, and then concatenating the registrations. Estimates of the hemodynamic response (HDR) for each of the five above-mentioned events were made by convolving the functional signal for each event with an assumed canonical HDR function. Individually averaged functional data were then resampled from native to spherical space for surface-based analysis, with subsequent application of a 20 iteration smoothing function. This level of smoothing is approximately equal to the surface-based application of a 6.6 mm full width at half-maximum smoothing kernel.

Three contrasts were performed at the individual subject level: the difference in BOLD signal change between correctly identified old and new items (i.e., SH plus SM vs CR), the difference in BOLD signal change between correctly identified and forgotten old items (i.e., SH plus SM vs

M), and the difference in BOLD signal change between correct and incorrect source identification (i.e., SH vs SM). Subjects with a total event bin size of <10 items were excluded from those contrasts that included that event ($N = 1$ control and 1 patient from the old vs new contrast; $N = 5$ controls and 3 patients from the old vs miss contrast; and $N = 4$ controls and 5 patients from the source identification contrast).

Within-group and between-group comparisons were generated for each contrast, with statistical significance based on a cluster-wise probability (CWP) threshold of 0.05, a standard approach for correcting for multiple comparisons in surface-based analyses (Hagler et al., 2006). This CWP approach was implemented within FreeSurfer by initially running 1000 Monte Carlo simulations of synthesized white Gaussian noise using the smoothing, resampling, and averaging parameters of the functional analyses. This allowed us to determine the likelihood that a cluster of a certain size would be found by chance for a given vertex-based threshold.

In addition to this standard surface-based analysis, a secondary region of interest (ROI)-based approach was used, using the three bilateral regions found to be significant in the old versus new group-level contrast in control subjects (dorsolateral prefrontal cortex, posterior parietal cortex, and medial parietal cortex/precuneus) (Cannistraro et al., 2004). A functional label generated at the group level was morphed from an average subject to each individual subject (Fischl et al., 1999a,b), and the percentage signal change, averaged across the entire region, relative to a baseline offset, was obtained for all event types (Fischl et al., 2004). These values were incorporated into a mixed-model repeated-measures ANOVA, which examined the main effects of three within-subject measures (hemisphere, region, condition), and one between-subject measure (diagnosis), as well as their interactions. In addition, these ROI data were used in *post hoc* manner to explore the frontal–parietal activity relationship as well as the relationship between activity and performance using Pearson’s correlation coefficient (two-tailed α of 0.05). Of note, by including data from the entirety of each individual’s functionally defined ROI, as opposed to using the single most strongly activated vertex, we

attempted to minimize the possibility of spurious correlations (Vul et al., 2009).

MEG acquisition. MEG data were acquired in a magnetically shielded room using a dc-SQUID Neuromag Vectorview system. This system is comprised of 306 channels arranged in triplets of two orthogonally paired planar gradiometers and one magnetometer, which together measure magnetic field strength at 102 locations across the scalp. The MEG signal at each location was sampled at 601 Hz and bandpass filtered (0.1–200 Hz) during acquisition. Eye movements were recorded using electro-oculogram (EOG) electrodes, and four head position indicator (HPI) coils were attached to each subject's head to determine head position relative to the MEG sensors. To construct a head coordinate system, three fiducial landmarks (nasion and bilateral preauricular points) were digitized using a three-dimensional digitizer (Polhemus), along with the locations of the HPI coils and a set of additional points on each subject's head. To aid in source localization, this coordinate system was aligned with an anatomic magnetic resonance image acquired from each subject (1.5 tesla Siemens Avanto Scanner) generated from an average of two high-resolution T1-weighted anatomical scans [MPRAGE sequence (TR, 2.7 ms; TE, 3.3 ms; flip angle, 7°)].

MEG postacquisition processing. Preprocessing and analysis of data were accomplished using MNE software developed at the Athinoula A. Martinos Center for Biomedical Imaging (Charlestown, MA) (<http://www.nmr.mgh.harvard.edu/martinos/userInfo/data/sofMNE.php>). Raw data were inspected visually and noisy channels were excluded from analysis. Two second epochs (plus a 200 ms prestimulus baseline) time-locked to stimulus onset were defined as the time window of interest. Waveforms within these time windows were additionally low-pass filtered at 30 Hz, and the baseline period 200 ms before stimulus onset was subtracted from each epoch before averaging. Epochs containing EOG amplitudes exceeding 300 μ V or gradiometer amplitudes exceeding 2000 fT/cm were excluded from the average. Averages for each event type (SH, SM, M, FA, CR) were calculated across trials within a run for an individual subject, and grand averages for each event type were calculated across runs for each subject. A minimum bin size of 25 total events per condition was set as a minimum threshold for a subject to be included in the analysis. To meet these minimum criteria, SH and SM responses were combined as a single event representing the correct identification of "old" items and averages were generated for this combined response category. Of the 15 controls and 16 patients who completed the MEG scan, one patient was excluded because of excessive noise artifact and one control and one patient were excluded because of inadequate bin sizes even after combining the SH and SM events as described above. This resulted in the inclusion of 14 controls and 14 patients in all subsequently described analyses.

MEG source space analysis. Three-dimensional cortical surface models were reconstructed from subjects' MR images using FreeSurfer software. Alignment of the MEG and MRI coordinate frames was accomplished manually by identifying the fiducial landmarks digitized on the subject's head using the high-resolution anatomic MR images described above. An ICP (iterative closest point) algorithm was then applied to fine-tune the locations of the additional digitized points. A single compartment (inner skull) BEM (boundary-element model) decimated to ~5000 dipole locations per hemisphere was used to calculate the forward solution. Inverse solutions of the MEG were calculated according to a MNE (minimum norm estimate) without depth weighting. All subjects' individual anatomical surfaces were averaged, and using a spherical morphing procedure, each subjects' inverse solution was projected onto this

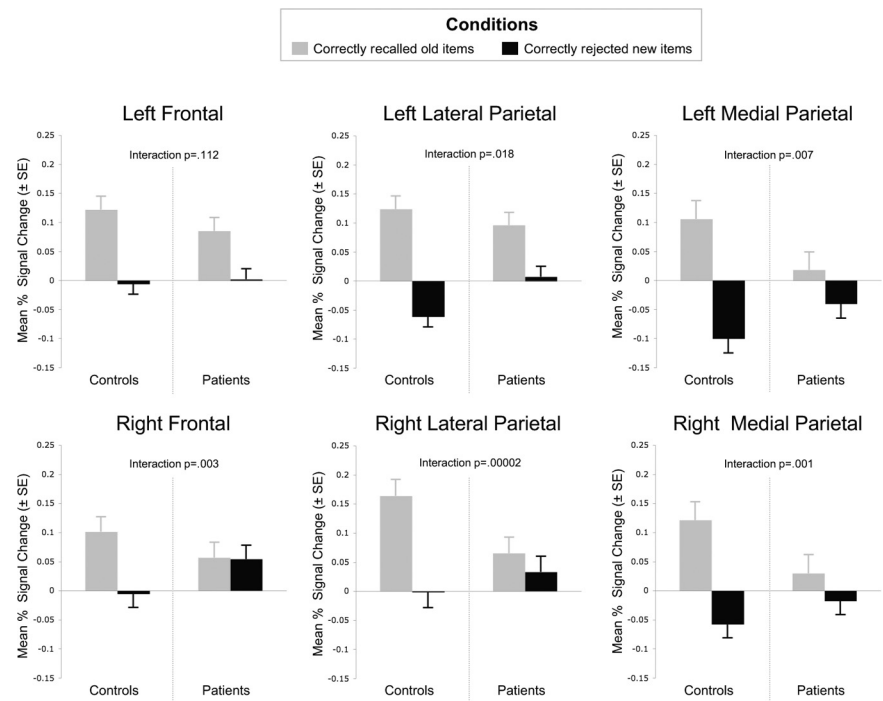


Figure 2. Bar charts illustrating the event-related percentage BOLD signal change within the three bilateral regions of interest (frontal, lateral parietal, and medial parietal). Error bars indicate SE. Values of p reflect diagnosis by condition interactions within each region. Note the strong old–new modulation seen in control subjects across each examined region, a pattern that is diminished or absent in the schizophrenia cohort.

common surface. This allowed within-group t tests to be performed (Moon et al., 2007), to investigate differences in electromagnetic response to the old and new conditions at each vertex on the surface. These t values were then visualized as within-group statistical maps of the old–new difference, using a vertex-wise α of 0.05.

To further evaluate the time course of old–new signal differences within the frontoparietal a priori ROIs, anatomically based ROIs were defined using an automated surface parcellation approach applied to the high-resolution magnetic resonance images (Fischl et al., 2004). Current estimates within these ROIs were then averaged to create group-level time courses for both old and new conditions. The so-called old–new effect consists of a greater electrical response to old items, relative to new items, beginning as early as 500 ms after stimulus presentation (Rugg and Curran, 2007). There are at least two temporally and regionally distinct aspects to this effect: one focused in the posterior parietal cortex (predominantly on the left), which extends from ~500–800 ms after stimulus (also known as a P600 or late positive complex), and one focused in the right prefrontal cortex, extending from ~600 to 1600 ms after stimulus (also known as a late frontal effect) (Rugg and Nagy, 1989; Friedman, 1990; Tendolkar et al., 2000; Rugg and Curran, 2007). Hence signal differences between correctly recalled old items and newly presented items were examined in this context, with a focus on the 500–800 ms period in the left posterior parietal cortex, and the 600–1600 ms period in the right prefrontal cortex.

To determine whether old–new differences existed outside the frontoparietal ROIs, an exploratory, cortex-wide analysis was conducted across all vertices. To control for multiple comparisons, an uncorrected threshold of $p < 0.001$ was used to identify significant clusters.

Results

Behavioral data

Behavioral data are summarized in Table 1. As reported previously (Weiss et al., 2008), during fMRI scans, control subjects were significantly more accurate in old–new recognition than patients with schizophrenia. When specifically examining the source accuracy of items deemed to be old (i.e., the percentage of

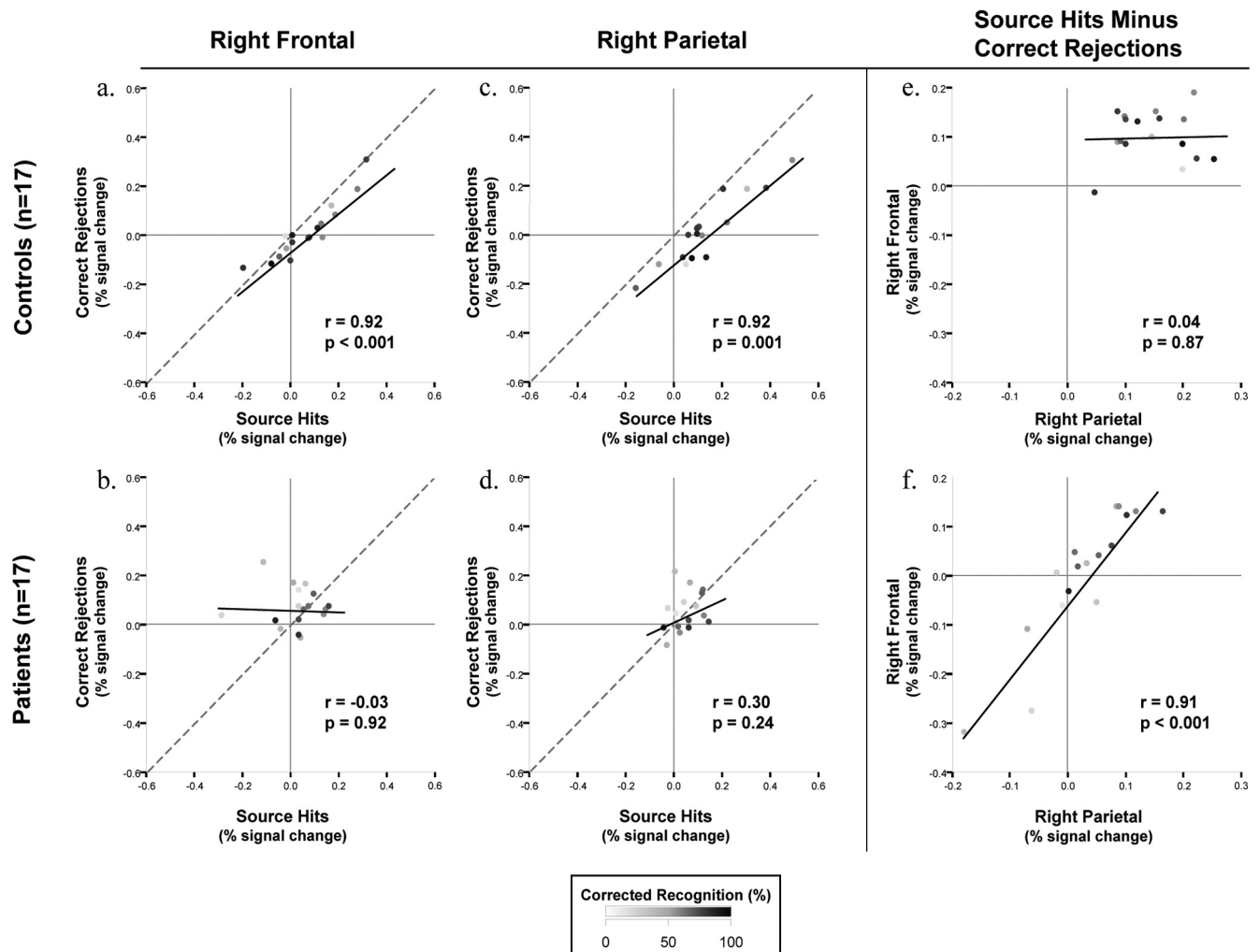


Figure 3. Scatter plots showing the within-region relationship between activity to correctly identified old and new events (*a–d*) and the between-region relationship for the degree of old–new activity difference. In control subjects (*a, c*), note the near-unanimous location of the points below the diagonal, indicating greater activity to source hits than correct rejections. Note also the extremely high correlation between the overall degree of signal change for each event across the control cohort—whatever the level of activity to source hits, there is a consistent “activity buffer” that physiologically distinguishes these events from correctly rejected new items. This degree of old–new difference is essentially a constant in both the right frontal and right parietal cortices, with little evidence for correlation across the two regions at the individual subject level (*e*). The pattern seen in patients with schizophrenia is entirely different (*b, d*). The tightly regulated activity relationship between source hits and correct rejections is abolished. We also see a large degree of variation around the diagonal, indicating that some patients show an old–new effect and some do not. Interestingly, the degree of old–new activity difference is strongly correlated across the two regions, with strong frontal lobe “activators” also being strong parietal lobe activators (*f*). Finally, the degree of old–new activity is significantly correlated with performance, as noted by the performance-based shading of the points. Patients who are strong activators tend to show better recognition memory performance (dark shading) when compared with those who are weak activators (light shading).

correct source responses for old items labeled either “male” or “female”), there were no significant differences between the two groups. Analogous results were obtained when subjects underwent the task during MEG scanning.

fMRI analyses

Old versus new

Within the control subjects, comparison of the BOLD signal change associated with the correct identification of an item as old with that associated with the correct rejection of an item as new revealed a bilateral pattern of significant differences within the superior and middle dorsolateral prefrontal cortex (DLPFC), the lateral posterior parietal cortex (mostly within the angular gyrus and intraparietal sulcus), and the medial parietal cortex/precuneus (Fig. 1; supplemental Table 1, available at www.jneurosci.org as supplemental material). Subjects with schizophrenia showed a similar pattern of old versus new activation differences within the left hemisphere, with significant clusters located in the

left DLPFC, posterior parietal cortex (angular gyrus and intraparietal sulcus), and the medial parietal cortex/precuneus. Unlike the control subjects, however, there were little to no old–new activation differences seen in the right hemisphere; indeed, the only clusters that met predetermined significance thresholds were deactivations located within the right superior, middle, and inferior temporal gyri. When the old–new effects seen in these two groups were compared directly, both the medial and lateral parietal cortices showed greater activity in control subjects, particularly within the right intraparietal sulcus and angular gyrus.

Old versus miss

The pattern of BOLD signal change differences between items correctly identified as old and items that were subsequently forgotten (i.e., misses) was similar to that seen in the old–new contrasts described above (supplemental Fig. 1, Table 2, available at www.jneurosci.org as supplemental material).

Current Estimates in Controls Left Parietal Lobe: Old vs New

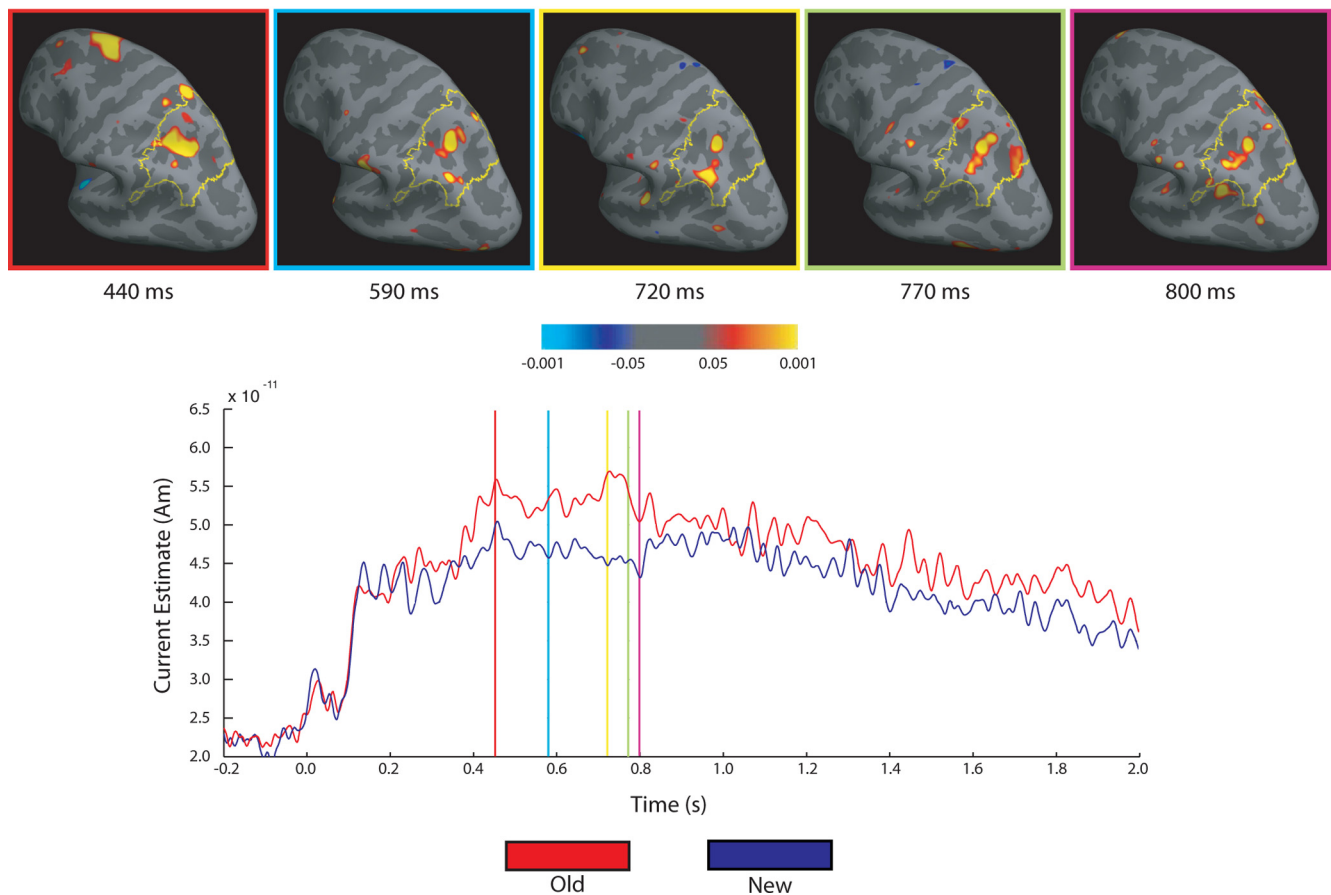


Figure 4. Source space analysis of left parietal old–new effect in controls. T-maps of the between condition difference in estimated current are displayed on inflated standard surfaces. Color coding represents statistical significance (p value) of this difference. The left posterior parietal cortex as anatomically defined by an automated parcellation approach is outlined in yellow. The group average signal (in ampere · meters) within this region is displayed below for both old and new conditions. Note the separation of the old and new time courses.

Source hits versus source misses

Neither control subjects nor patients with schizophrenia exhibited significant clusters of activation difference when correct versus incorrect source memory performance were compared directly. There were no significant regions demonstrating between-group activation differences for this contrast.

Region of interest-based analyses

The bilateral set of regions showing the greatest old–new effect in the healthy control population (DLPFC, lateral parietal cortex, and medial parietal cortex/precuneus) were identified as functionally defined regions of interest and the percentage BOLD signal change during the old and new conditions [i.e., (SH plus SM) vs CR] within each region was computed (Fig. 2). These values were then entered into a repeated measures ANOVA to look for main effects of condition [(SH plus SM) vs CR], hemisphere (left vs right), region (DLPFC, lateral parietal, and medial parietal/precuneus), and group (control vs schizophrenia) and the interactions between these effects. This analysis demonstrated a significant main effect for condition ($F_{(1,32)} = 60.4$; $p < 0.000001$) and region ($F_{(2,64)} = 8.86$; $p = 0.0004$), but not for diagnostic group ($F_{(1,32)} = 0.18$; $p = 0.68$). Of relevance here, there was a significant group by condition interaction ($F_{(1,32)} = 15.9$; $p = 0.0004$), as well as a group by condition by hemisphere by region interaction ($F_{(2,64)} = 3.38$; $p = 0.04$). Follow-up analyses conducted within each of the six regions of interest indicated

significant group by condition interactions in all regions except for the left DLPFC: left DLPFC ($F_{(1,32)} = 2.67$; $p = 0.112$), right DLPFC ($F_{(1,32)} = 9.97$; $p = 0.003$), left lateral parietal ($F_{(1,32)} = 6.23$; $p = 0.018$), right lateral parietal ($F_{(1,32)} = 25.1$; $p = 0.00002$), left medial parietal ($F_{(1,32)} = 8.40$; $p = 0.007$), and right medial parietal ($F_{(1,32)} = 12.5$; $p = 0.001$). In each of the five significant regions, old–new differences were greater in controls than in patients.

Frontal–parietal correlations

To better understand the interrelationship between frontal and parietal old–new activation seen in these two groups, the ROI-based percentage signal change values were entered into a series of *post hoc* bivariate correlation analyses. In control subjects, there was a strong positive correlation between the degree of activation during correctly identified old items (source hits) and correctly rejected new items within a particular region (Fig. 3*a–c*). Thus, within both the right DLPFC ($r = 0.92$; $p < 0.000001$) and right lateral parietal cortex ($r = 0.92$; $p < 0.000001$), the degree of BOLD signal change during source hits was tightly correlated with the degree of BOLD signal change during correct rejections. However, the degree of activity between these two regions did not show a significant correlation in control subjects; neither for source hits ($r = 0.46$; $p = 0.06$) nor for correct rejections ($r = 0.38$; $p = 0.13$) (figures not shown). Overall, therefore, control subjects show a pattern in which there is consistent difference

Current Estimates in Patients Left Parietal Lobe: Old vs New

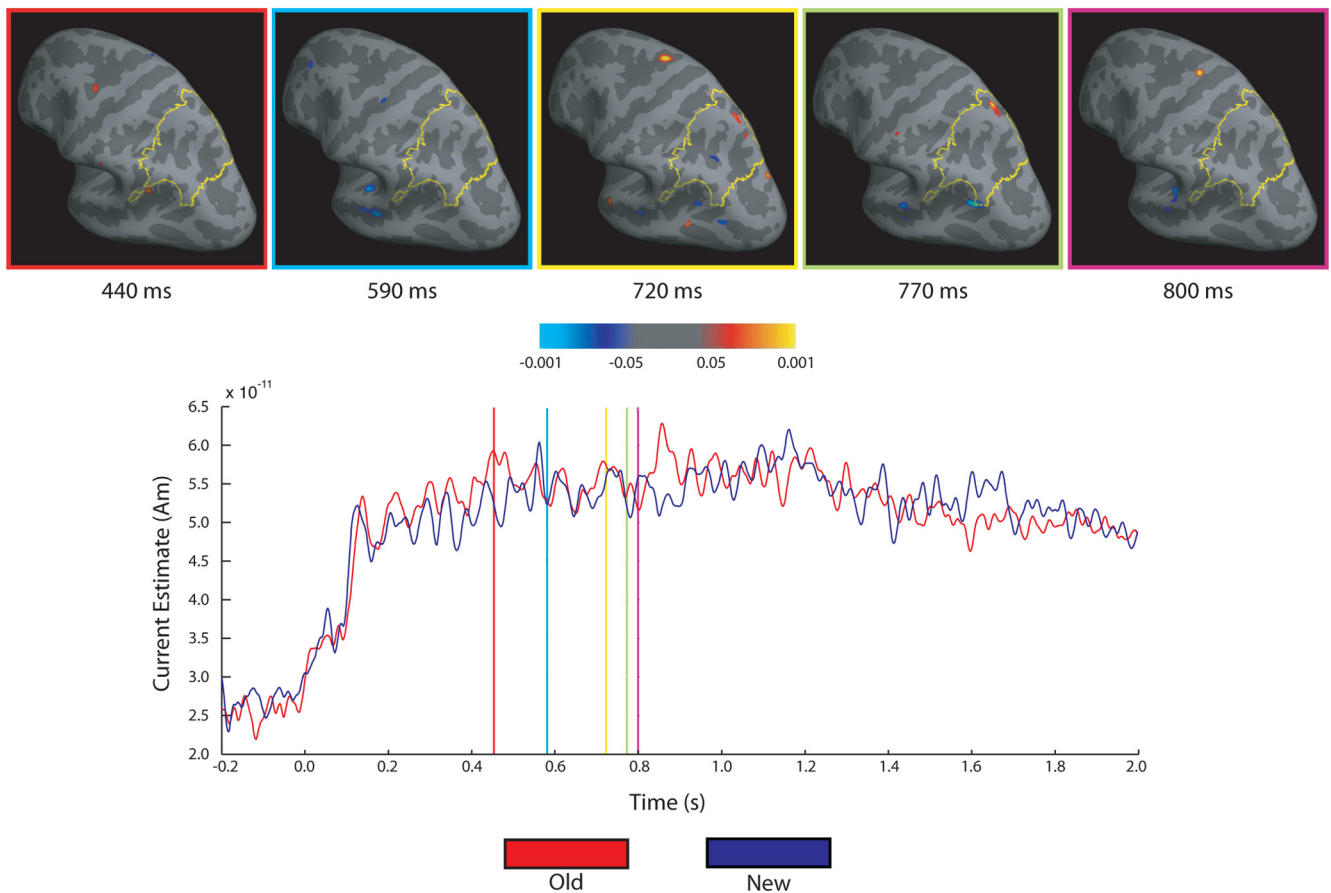


Figure 5. Source space analysis of left parietal old–new effect in patients. Group average signal within the left posterior parietal cortex is displayed on inflated cortical surfaces for both old and new conditions, as in Figure 4. Note the lack of separation of the old and new time courses.

between correctly identified old and new items in both frontal and parietal regions, but the degree of overall activity across these two regions is less tightly correlated.

The pattern seen in the patients with schizophrenia was precisely opposite to that seen in controls. In patients, there was no significant within-region correlation between source hits and correct rejections, neither in the frontal ($r = -0.03$; $p = 0.92$) nor lateral parietal ($r = 0.30$; $p = 0.24$) cortices (Fig. 3*b,d*). Thus, the degree of activation to one condition was not predictive of the degree of activity to the other condition within a single region. However, for a specific condition, there was a strong positive correlation between the frontal and parietal lobe activation pattern, true for both source hits ($r = 0.67$; $p = 0.003$) and correct rejections ($r = 0.83$; $p = 0.00005$) (figures not shown).

Finally, unlike control subjects in which the degree of old–new difference was practically a constant in both frontal and parietal regions (with no between-region correlation: $r = 0.04$; $p = 0.87$) (Fig. 3*e*), in patients there was an extraordinarily tight positive relationship between the degree of old–new differences seen in the right frontal lobe and that seen in the right parietal lobe at the individual subject level ($r = 0.91$; $p = 0.000001$) (Fig. 3*f*). Similarly, correlations were found between the left parietal and right frontal region in patients ($r = 0.65$; $p = 0.004$) but not controls ($r = 0.00$; $p = 1.00$) (data not shown). Importantly, there was a strong relationship in patients between the degree of old–new activation difference and recognition memory performance (as

measured by corrected recognition), in both the right frontal ($r = 0.53$; $p = 0.03$) and right parietal ($r = 0.50$; $p = 0.04$) regions of interest (figures not shown).

There was no correlation between the degree of old–new BOLD signal difference and clinical severity (as measured by both SAPS and SANS) in any of the bilaterally defined regions of interest (maximal correlation was between old–new difference in the left frontal region and SAPS score, $r = -0.27$; $p = 0.29$). Similarly, no region showed a correlation between the degree of old–new BOLD signal difference and medication burden (based on chlorpromazine equivalents) (maximal correlation was in the left frontal region, $r = -0.43$; $p = 0.09$).

MEG source space analyses

Parietal lobe

As anticipated, control subjects showed a strong old–new difference in estimated cortical electrical activity within the left posterior parietal lobe, centered on an area consistent with the intraparietal sulcus (Fig. 4). Separation in the electrical response began at ~ 400 ms after stimulus and was sustained until ~ 800 ms after stimulus. During this time window, tests of between-condition difference (old > new) showed consistent evidence for statistically significant clusters (at $p < 0.001$). Control subjects did not demonstrate the same degree of old–new separation within the right parietal cortex; occasional significant clusters were present, but they were small and widely interspersed in time.

Current Estimates in Controls Right Frontal Lobe: Old vs New

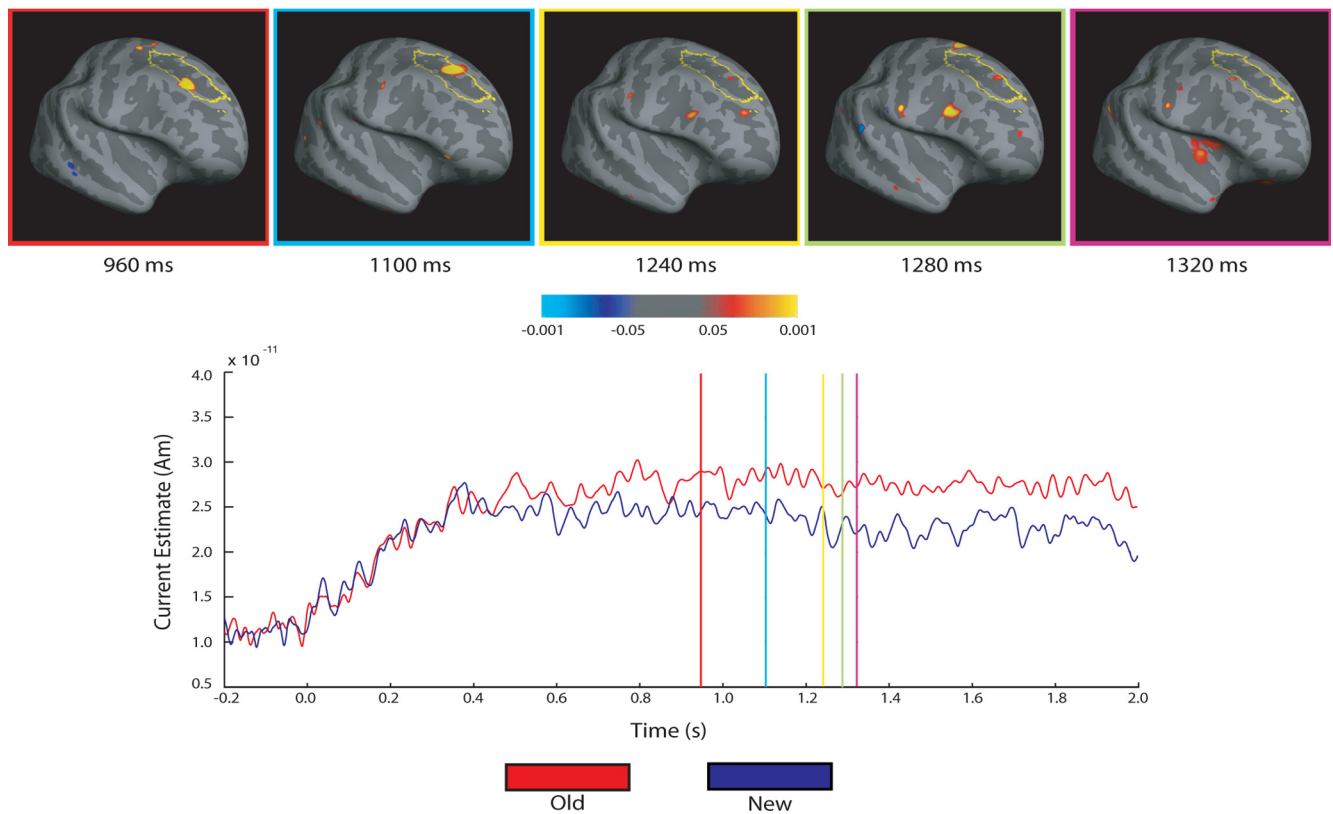


Figure 6. Source space analysis of right frontal old–new effect in controls. T-maps of the between condition difference in estimated current are displayed on inflated standard surfaces. Color coding represents statistical significance (p value) of this difference. The right superior frontal gyrus as anatomically defined by an automated parcellation approach is outlined in yellow. The group average signal within this region (in ampere \cdot meters) is displayed below for both old and new conditions. Note, in controls, the strong old–new effect within the superior frontal gyrus that decreases in significance later over the time course.

Unlike the strong old–new separation seen in the controls, patients with schizophrenia showed no evidence for a parietal old–new effect, neither in the left nor right hemispheres. As seen in Figure 5, the estimated cortical electrical response to these two event types was mostly overlapping throughout the recording period. When compared with control subjects, patients demonstrated a similar degree of electrical activity to the old items, with an average current estimate of ~ 5.4 to 5.5×10^{11} ampere \cdot meters (Am) in both groups during the 500–800 ms poststimulus time window. But in contradistinction to control subjects, patients did not downregulate this activity during the correct rejection of new items; their average current estimates in response to these events remained at $\sim 5.5 \times 10^{11}$ Am, whereas it was nearly a full unit lower in control subjects.

Frontal lobe

Control subjects also demonstrated a significant old–new effect within the right superior frontal lobe (Fig. 6). The electrical response to these two events diverged at ~ 600 ms after stimulus and showed a sustained difference throughout the remainder of the time course. Statistically significant clusters were evident at several points throughout the period, most substantially during the 900–1200 ms poststimulus time frame.

Patients with schizophrenia did not demonstrate this right frontal old–new effect (Fig. 7). In fact, beginning at ~ 700 ms after stimulus, there was a reversal pattern seen in this cohort, with correctly rejected new items eliciting a more robust electrical response than correctly recognized old items. This new–old dif-

ference was apparent throughout the remainder of the time course, with statistically significant clusters becoming most apparent during the 1200–1300 ms poststimulus time frame. Once again, the response to old items was relatively similar when compared between the two groups, whereas the response to new items showed a more marked amplitude difference.

Superior and middle temporal gyri

Although the patients with schizophrenia did not demonstrate the expected old–new differences within the frontoparietal regions of a priori interest, an exploratory inspection of cortical regions outside of these areas revealed a dramatic pattern of activity difference within the auditory-related cortical regions bilaterally (Fig. 8). Within the left superior and middle temporal lobes, patients showed a robust pattern of new $>$ old activity, which began at ~ 400 ms after stimulus and terminated at ~ 900 ms after stimulus. At about that point, the patients then show a robust old $>$ new effect within the corresponding regions in the right hemisphere, an effect that was sustained until ~ 1300 ms after stimulus. Control subjects did not demonstrate these patterns, with statistically equivalent old and new responses within the temporal cortices of both hemispheres (data not shown).

Discussion

Differentiating new from previously presented items is a basic and critically important element of recognition memory, one that appears to be disrupted in schizophrenia. Using multimodal imaging techniques, we have demonstrated in this investigation

Current Estimates in Patients Right Frontal Lobe: Old vs New

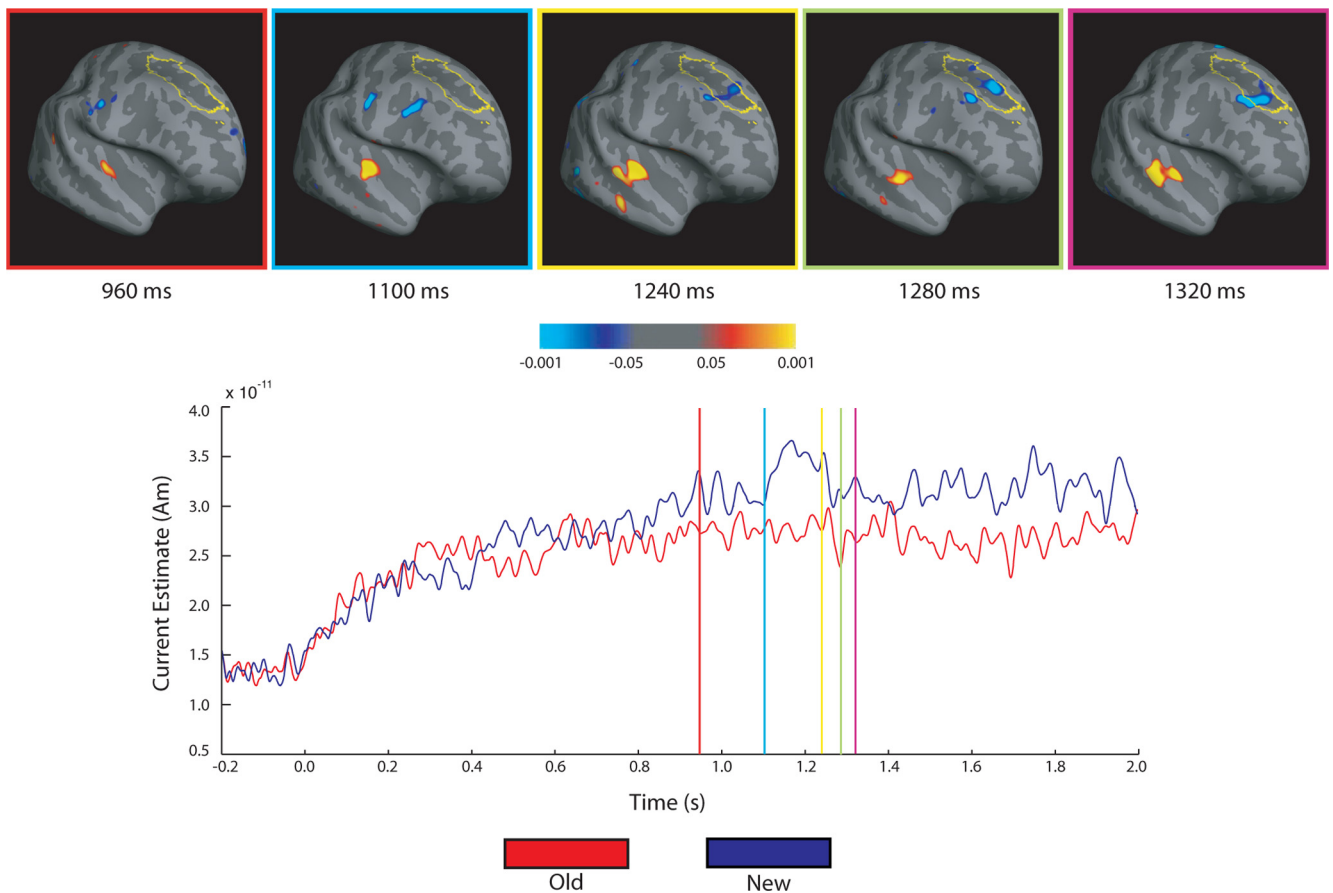


Figure 7. Source space analysis of right frontal old–new effect in patients. Group average signal within the right superior frontal gyrus is displayed on inflated cortical surfaces for both old and new conditions, as in Figure 6. Note that, in patients, there is a complete reversal of the effect seen in controls over the same time course. Rather, patients exhibit a “new–old” effect that increases in significance across the time course.

that the neural physiology underlying old–new item distinction differs substantially between schizophrenia patients and healthy control subjects. The two principal findings are summarized as follows: (1) In the context of poorer recognition memory performance, patients with schizophrenia showed either a diminished or absent old–new effect within the frontoparietal network, particularly within the right hemisphere. Those patients who did show a “normal” physiological response pattern (i.e., greater BOLD signal for old vs new) also showed a normal level of recognition memory performance. (2) As seen with the finer temporal resolution of MEG, control subjects exhibited a sequential pattern of old > new electrical activity first in the left posterior parietal cortex and then right prefrontal cortex, consistent with previous reports, whereas no such differences were found in patients.

The strong frontoparietal old–new effect in control subjects is consistent with a relatively large fMRI literature documenting the importance of these regions in normal episodic memory processes (Nolde et al., 1998; Konishi et al., 2000; Dobbins et al., 2003; Leube et al., 2003; Maril et al., 2003; Kahn et al., 2004; Wheeler and Buckner, 2004; Hofer et al., 2007) (for relevant recent reviews, see Wagner et al., 2005; Skinner and Fernandes, 2007; Cabeza et al., 2008). Previous fMRI studies of the old–new effect in patients with schizophrenia have also identified aberrant modulation of both frontal and parietal lobe regions, although

both frontoparietal hypoactivity (Weiss et al., 2006) and hyperactivity (Ragland et al., 2004) have been associated with task performance.

Consistent with a large body of previous ERP research (Rugg and Curran, 2007), as well as two previous MEG reports (Tendolkar et al., 2000; Walla et al., 2005), healthy control subjects showed a clear differential response to old and new items beginning first in the inferior parietal cortex at ~400–500 ms after stimulus, followed by the right superior frontal gyrus (400–1600 ms after stimulus). In contrast to the healthy subjects in these studies, as well as our control population, the patients in our study showed neither the left posterior parietal nor the right superior prefrontal old–new effects. Although to our knowledge this represents the first study to use MEG to examine this effect in patients with schizophrenia, a body of ERP literature on this topic does exist (Kayser et al., 1999; Matsuoka et al., 1999; Guillem et al., 2001, 2003; Matsumoto et al., 2001; Tendolkar et al., 2002; Kim et al., 2004). Of these, the study by Tendolkar et al. is most similar to the present report in that it tested recognition memory for words using discrete study and test blocks. In comparison with a control population, they found that patients with schizophrenia demonstrated temporally truncated old–new effects (frontal and parietal) in association with consciously recalled responses, and a lack of a parietal lobe old–new effect to items that were only associated with a sense of familiarity.

Current Estimates in Patients Temporal Lobes: Old vs New

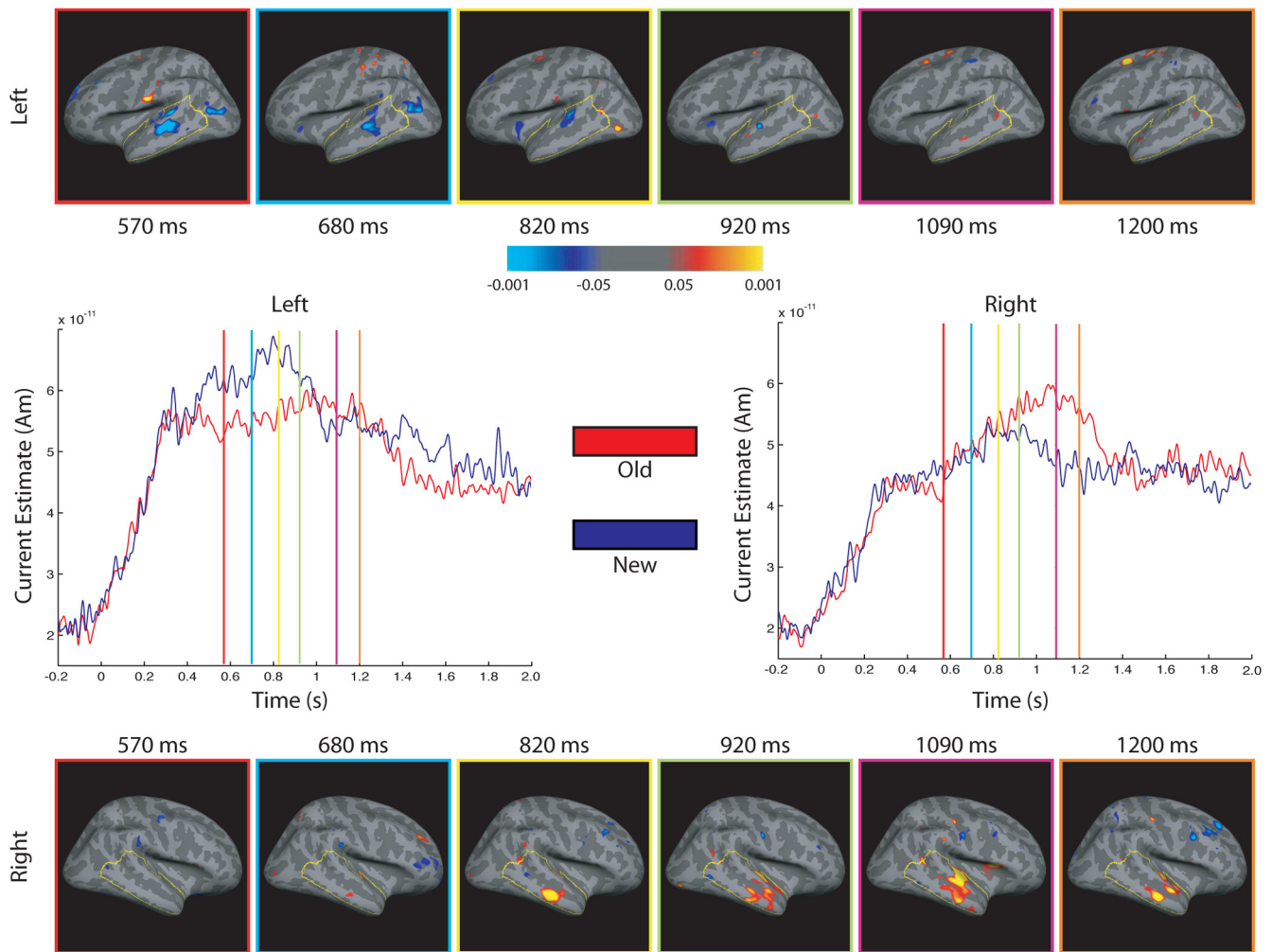


Figure 8. Source space analysis of left and right temporal lobe (patients). T-maps of the between-condition difference in estimated current are displayed on inflated standard surfaces. Color coding represents statistical significance (p value) of this difference. The left and right superior and middle temporal gyri as anatomically defined by an automated parcellation approach are outlined in yellow. The group average signals within both left and right regions (in ampere \cdot meters) are displayed below for both old and new conditions. Note the reverse patterns of activity occurring between the two hemispheres in which the left displays a new–old effect occurring earlier than the old–new effect in the right hemisphere of the patients.

Collectively, the present fMRI and MEG findings are consistent with markedly different distributions of regional specialization necessary to complete the task in patients versus controls. In healthy subjects, the old > new electrical signal that we and others have observed in the left posterior parietal cortex has generally been thought to reflect recollective processes, as the effect has been shown to be sensitive to accurate source judgment as well as linked to the subjective experience of conscious retrieval (compared with familiarity) using the remember–know paradigm (Düzel et al., 1997; Donaldson and Rugg, 1999; Curran, 2000; Curran et al., 2001; Duarte et al., 2004). The predominantly right-sided late frontal old–new effect has also been generally linked to recollective processes, such as those required for accurate source or associative memory (Wilding and Rugg, 1996; Allan and Rugg, 1998; Allan et al., 2000). A number of studies have alternatively or additionally linked this physiologic marker to postretrieval monitoring, with some recent evidence suggesting that the effect is more associated to general monitoring or decision making, rather than being a retrieval-specific component (Dobbins and Han, 2006; Hayama et al., 2008). Such goal-directed activity at different times, in different regions, even in different hemi-

spheres, suggests a highly regionally specialized use of information. Similarly, the bilateral activation of both frontal and parietal regions coupled with a lack of correlation between them, as seen with fMRI, suggests that these regions are each engaged in components of the old–new item distinction process, but that those components differ between regions.

In patients, however, the lack of distinction between old and new items as seen in the left parietal and right frontal MEG recordings during their respective critical time periods suggests a failure of these regions to distinguish old and new items (despite their engagement in the task, as suggested by the rise in signal above baseline). As suggested by their highly correlated BOLD signal, however, these regions may be working in a coordinated way to facilitate task performance, which is, after all, intact in the events included in this analysis. Furthermore, the temporal lobe MEG findings, unique to patients, suggests that recruitment of another region (one not normally associated with old–new item distinction) may be necessary for successful performance in patients. This explanation would be consistent with the work of Ragland and colleagues (Ragland et al., 2004; Ragland et al., 2006; Wolf et al., 2007), who have suggested that the enhanced fronto-

temporal connectivity and temporal lobe hyperactivity seen during recognition memory in patients with schizophrenia, are signs of a (ineffective) compensatory mechanism. Although speculative, it may also be possible that the absence of the frontoparietal old–new effect diminishes the sense of confidence that patients have in their response, a widely reported finding within the schizophrenia memory literature (Bacon et al., 2001; Moritz and Woodward, 2002, 2006; Moritz et al., 2003, 2005; Kircher et al., 2007). Indeed, individuals with parietal lobe lesions have been found to have intact episodic memory (including source memory) but impaired confidence in or vividness of the recollected material (Berryhill et al., 2007; Davidson et al., 2008; Simons et al., 2008). Additional study, directly measuring memory confidence in conjunction with neuroimaging data in patients with schizophrenia, would be necessary to test this hypothesis.

It is important to note that frontoparietal activation may not be specific to episodic memory performance. These regions are in fact associated with a wide variety of cognitive tasks, including working memory, executive function, and conscious visual perception (Naghavi and Nyberg, 2005). It remains possible that the frontoparietal abnormalities seen in the present study are related to a broader and cross-cutting cognitive construct, such as cognitive control (MacDonald et al., 2000) or the allocation of attention (Cabeza et al., 2008), rather than specifically and solely to episodic memory performance. Indeed, this may help explain why deficient activation of these areas has been associated with a number of cognitive impairments in schizophrenia, including transitive inference (Ongür et al., 2006), semantic recall (Assaf et al., 2006), working memory (Barch and Csernansky, 2007), visual attention (Gur et al., 2007), and response suppression (Ford et al., 2004).

The inclusion of medicated patients with schizophrenia represents the primary limitation of the present study. As dopamine may play a role in the detection and response to novelty (Lisman and Grace, 2005), we cannot fully exclude the possibility that medication with dopamine antagonists may have contributed to the abnormalities in stimulus-related signal reported here. This seems unlikely for a number of reasons. First, there was no correlation between medication burden and either memory performance or the degree of old–new BOLD signal difference in any of the six ROIs examined. Second, based on a recent review of the literature it appears that the longitudinal use of antipsychotic medications is more often associated with normalization of cerebral activity, although substantial methodological differences preclude confident conclusions at this time (Davis et al., 2005). Furthermore, the pattern of task-related dorsolateral prefrontal cortex hypoactivity seen in patients with schizophrenia has been shown to be unaffected by the initiation of antipsychotic medication (Snitz et al., 2005).

This issue notwithstanding, the results presented here indicate an important physiological correlate of aberrant cognitive performance in patients with schizophrenia. Additional work is necessary to better understand the interindividual variance in performance and physiology seen within the patient cohort. In particular, the potential role of genetic polymorphisms now known to affect the activity of this frontoparietal circuit (Tan et al., 2007a) would be of substantial interest.

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