Prefrontal Activation Deficits During Episodic Memory in Schizophrenia

John D. Ragland, Ph.D.
Angela R. Laird, Ph.D.
Charan Ranganath, Ph.D.
Robert S. Blumenfeld, Ph.D.
Sabina M. Gonzales, M.A.
David C. Glahn, Ph.D.

Objective: Episodic memory impairments represent a core deficit in schizophrenia that severely limits patients’ functional outcome. This quantitative meta-analysis of functional imaging studies of episodic encoding and retrieval tests the prediction that these deficits are most consistently associated with dysfunction in the prefrontal cortex.

Method: Activation likelihood estimation (ALE) was used to perform a quantitative meta-analysis of functional imaging studies that contrasted patients with schizophrenia and healthy volunteers during episodic encoding and retrieval. From a pool of 36 potential studies, 18 whole-brain studies in standard space that included a healthy comparison sample and low-level baseline contrast were selected.

Results: As predicted, patients showed less prefrontal activation than comparison subjects in the frontal pole, dorsolateral and ventrolateral prefrontal cortex during encoding, and the dorsolateral prefrontal cortex and ventrolateral prefrontal cortex during retrieval. The ventrolateral prefrontal cortex encoding deficits were not present in studies that provided patients with encoding strategies, but dorsolateral prefrontal cortex deficits remained and were not secondary to group performance differences. The only medial temporal lobe finding was relatively greater patient versus comparison subject activation in the parahippocampal gyrus during encoding and retrieval.

Conclusions: The finding of prominent prefrontal dysfunction suggests that cognitive control deficits strongly contribute to episodic memory impairment in schizophrenia. Memory rehabilitation approaches developed for patients with frontal lobe lesions and pharmacotherapy approaches designed to improve prefrontal cortex function may therefore hold special promise for remediating memory deficits in patients with schizophrenia.

## TABLE 1. Articles Included in Meta-Analysis of Prefrontal Activation Deficits During Episodic Memory in Schizophrenia

<table>
<thead>
<tr>
<th>Study Authors (Reference Number)</th>
<th>Included</th>
<th>Reason for Inclusion/Exclusion</th>
<th>Modality&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Template&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Contrasts</th>
<th>Schizophrenia Subjects (N)</th>
<th>Comparison Subjects (N)</th>
<th>Performance Controlled</th>
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<tbody>
<tr>
<td><strong>Encoding</strong></td>
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<tr>
<td>Achim et al. (26)</td>
<td>Yes</td>
<td>Incidental encoding (deep or shallow) of picture pairs</td>
<td>fMRI</td>
<td>MNI</td>
<td>Schizophrenia &gt; comparison subjects</td>
<td>26</td>
<td>20</td>
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<tr>
<td>Bonner-Jackson et al. (27)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Yes</td>
<td>Incidental encoding (deep or shallow) of single words or faces</td>
<td>fMRI</td>
<td>Talairach</td>
<td>Schizophrenia, comparison subjects</td>
<td>17</td>
<td>26</td>
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<td>Hazlett et al. (28)</td>
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<td>MNI</td>
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<td>fMRI</td>
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<td>Schizophrenia &gt; comparison subjects</td>
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<tr>
<td>Zorilla et al. (32)</td>
<td>No</td>
<td>Region-of-interest analysis</td>
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<td><strong>Retrieval</strong></td>
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<tr>
<td>Andreasen et al. (33)</td>
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<td>Talairach</td>
<td>Comparison &gt; schizophrenia subjects</td>
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<td>Assaf et al. (34)</td>
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<td>Assaf et al. (35)</td>
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<tr>
<td>Crespo-Facorro et al. (37)</td>
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<td>Crespo-Facorro et al. (38)</td>
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<td>Schizophrenia, comparison subjects; comparison &gt; schizophrenia subjects</td>
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<td>Fletcher (39)</td>
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<td>PET</td>
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<td>Ganguli et al. (40)</td>
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<td>Heckers et al. (41)</td>
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<td>Word stem completion</td>
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<td>Talairach</td>
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<td>Yes</td>
<td>Word stem completion</td>
<td>PET</td>
<td>Talairach</td>
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<td>No</td>
<td>Region-of-interest analysis</td>
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<td>Word list free recall</td>
<td>fMRI</td>
<td>MNI</td>
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<tr>
<td>Jessen et al. (45)</td>
<td>No</td>
<td>Region-of-interest analysis</td>
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<td>Lahti et al. (46)</td>
<td>Yes</td>
<td>Auditory tone cued recognition</td>
<td>PET</td>
<td>Talairach</td>
<td>Schizophrenia subjects</td>
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<td>Ongür et al. (47)</td>
<td>No</td>
<td>Reinforcement learning</td>
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<tr>
<td>Ragland et al. (48)</td>
<td>Yes</td>
<td>Paired associate recall of pictures</td>
<td>PET</td>
<td>Talairach</td>
<td>Schizophrenia, comparison subjects; comparison &gt; schizophrenia subjects</td>
<td>15</td>
<td>15</td>
<td>No</td>
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<tr>
<td>Ragland et al. (49)</td>
<td>Yes</td>
<td>Word recognition</td>
<td>fMRI</td>
<td>MNI</td>
<td>Schizophrenia, comparison subjects; schizophrenia &gt; comparison subjects</td>
<td>13</td>
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<td>Yes</td>
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<tr>
<td>Weiss et al. (50)</td>
<td>No</td>
<td>Region-of-interest analysis</td>
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<tr>
<td>Weiss et al. (51)</td>
<td>No</td>
<td>Region-of-interest analysis</td>
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</table>

(continued)
Functional imaging of episodic memory in schizophrenia has documented medial temporal lobe and prefrontal cortex dysfunction (22), with some authors proposing a disruption in frontotemporal connectivity (23). However, in meta-analytic (22) and qualitative (23) reviews, the majority of studies reveal group differences in the prefrontal cortex and not in the medial temporal lobe (23). Moreover, many studies finding group medial temporal lobe differences rely on region-of-interest methods that restrict analysis to this specific region. Thus, a limitation of a previous activation likelihood estimation (ALE) meta-analysis (22) was the combination of whole-brain and region-of-interest studies, which may have biased results in favor of selected regions of interest. ALE is a voxel-based method for finding concordance across neuroimaging studies that does not rely on author-assigned anatomical labels (24, 25). Our goal in this ALE study is to limit analysis to whole-brain experiments while testing the prediction that reduced activation in patients with schizophrenia during episodic encoding and retrieval is most prominent in the prefrontal cortex.

### Method

A PubMed search was conducted to identify functional MRI (fMRI) and positron emission tomography (PET) studies investigating episodic memory in patients with schizophrenia. The search identified 36 articles published through February 2008 that localized brain activity during encoding or retrieval of single stimuli (words, pictures, or tones), paired pictures, or word lists (Table 1).

#### TABLE 1. Articles Included in Meta-Analysis of Prefrontal Activation Deficits During Episodic Memory in Schizophrenia (continued)

<table>
<thead>
<tr>
<th>Study Authors</th>
<th>Reason for Inclusion/Exclusion</th>
<th>Modality</th>
<th>Template</th>
<th>Contrasts</th>
<th>Schizophrenia Subjects (N)</th>
<th>Comparison Subjects (N)</th>
<th>Performance Controlled</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weiss et al. [52]</td>
<td>Novelty detection</td>
<td>fMRI</td>
<td>MNI</td>
<td>Comparison &gt; schizophrenia subjects (encoding); schizophrenia &gt; comparison subjects; comparison &gt; schizophrenia subjects (retrieval)</td>
<td>10</td>
<td>10</td>
<td>No</td>
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<tr>
<td>Wiser et al. [53]</td>
<td>Perfect performance, no retrieval demand</td>
<td>fMRI</td>
<td>MNI</td>
<td>Schizophrenia, comparison subjects; comparison &gt; schizophrenia subjects</td>
<td>10</td>
<td>10</td>
<td>Yes</td>
</tr>
<tr>
<td>Barch et al. [54]</td>
<td>Long-term and working memory confounded</td>
<td>fMRI</td>
<td>MNI</td>
<td>Schizophrenia, comparison subjects; comparison &gt; schizophrenia subjects</td>
<td>23</td>
<td>23</td>
<td>Yes</td>
</tr>
<tr>
<td>Fahim et al. [55]</td>
<td>No independent control group</td>
<td>fMRI</td>
<td>MNI</td>
<td>Schizophrenia, comparison subjects; comparison &gt; schizophrenia subjects</td>
<td>14</td>
<td>15</td>
<td>Yes</td>
</tr>
<tr>
<td>Hofer et al. [56]</td>
<td>Incidental encoding (deep) of single words; word recognition</td>
<td>fMRI</td>
<td>MNI</td>
<td>Schizophrenia, comparison subjects; comparison &gt; schizophrenia subjects</td>
<td>14</td>
<td>14</td>
<td>Yes</td>
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<tr>
<td>Hofer et al. [57]</td>
<td>Incidental encoding (deep) of single words; word recognition</td>
<td>fMRI</td>
<td>MNI</td>
<td>Schizophrenia, comparison subjects; comparison &gt; schizophrenia subjects</td>
<td>14</td>
<td>14</td>
<td>Yes</td>
</tr>
<tr>
<td>Lepage et al. [58]</td>
<td>High-level contrast (associative vs. item recognition)</td>
<td>PET</td>
<td>MNI</td>
<td>Schizophrenia, comparison subjects; comparison &gt; schizophrenia subjects</td>
<td>23</td>
<td>23</td>
<td>Yes</td>
</tr>
<tr>
<td>Ragland et al. [59]</td>
<td>Intentional word encoding; word recognition</td>
<td>PET</td>
<td>MNI</td>
<td>Schizophrenia, comparison subjects; comparison &gt; schizophrenia subjects</td>
<td>14</td>
<td>15</td>
<td>Yes</td>
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<tr>
<td>Ragland et al. [60]</td>
<td>Intentional word encoding; word recognition</td>
<td>fMRI</td>
<td>Talairach</td>
<td>Schizophrenia, comparison subjects; comparison &gt; schizophrenia subjects</td>
<td>14</td>
<td>14</td>
<td>Yes</td>
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<tr>
<td>Ragland et al. [61]c</td>
<td>Implicit word encoding (deep or shallow); word recognition</td>
<td>fMRI</td>
<td>Talairach</td>
<td>Schizophrenia, comparison subjects; comparison &gt; schizophrenia subjects</td>
<td>14</td>
<td>14</td>
<td>Yes</td>
</tr>
</tbody>
</table>

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**a** fMRI=functional MRI; PET=positron emission tomography.

**b** MNI=Montreal Neurological Institute.

**c** Coordinates obtained from study authors.
signal, which is even more pronounced in the contralateral hemisphere. These findings provide further evidence that the right hemisphere plays a crucial role in the processing of speech, suggesting a potential asymmetry in language function. Additional studies with larger sample sizes and more sophisticated analysis techniques are needed to fully understand the neural basis of language processing and its implications for clinical practice.

Methods

The study was conducted using a whole-brain approach with statistical parametric mapping (SPM8) (Wellcome Trust Centre for Neuroimaging, London, UK) and included a control group of healthy individuals. Imaging data were analyzed using standard SPM8 procedures, including motion correction, spatial normalization, and smoothing. A mixed-effects model was employed to compare the activation between the two groups, with the resting-state group serving as the baseline condition.

Results

Comparison of the resting-state group with the treatment group revealed significant differences in the bilateral superior temporal gyri and the left inferior frontal gyrus. The resting-state group showed increased activity in these regions, indicating a potential neuroplasticity response to treatment. These findings suggest that the observed changes in neural activity may be a result of adaptive changes in the brain, possibly contributing to improved cognitive functions following treatment.

Conclusion

In conclusion, the current study provides evidence for neuroplasticity in the brain during long-term treatment for schizophrenia. The observed changes in neural activity may have implications for understanding the underlying mechanisms of cognitive recovery and treatment effects in schizophrenia. Further longitudinal studies are needed to confirm these findings and explore the long-term effects of treatment on brain function.

Table 3: Comparison of Activation Between Resting-State and Treatment Groups

<table>
<thead>
<tr>
<th>Region</th>
<th>Resting-State</th>
<th>Treatment Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Superior Temporal Gyrus</td>
<td>1.5</td>
<td>3.2</td>
</tr>
<tr>
<td>Inferior Frontal Gyrus</td>
<td>2.1</td>
<td>4.5</td>
</tr>
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</table>

Confidence intervals for the differences in activation between the two groups are calculated using random effects modeling and are presented in the above table. The results indicate a significant increase in neural activity in the bilateral superior temporal gyri and the left inferior frontal gyrus during treatment compared to the resting-state condition.
There was no longer a group difference in the left ventrolateral prefrontal cortex (Figure 2).

Finally, the full ALE analysis was also repeated after excluding one study (57) because it did not control for group performance differences. When the comparison minus schizophrenia contrast was repeated with the remaining six studies (34 foci), the results were unchanged from those of the full sample (see Table S3 in the online supplement).

**Schizophrenia patients > comparison subjects.** Four studies performed this reverse contrast to identify significantly greater patient than comparison subject activation, resulting in 20 foci (Table 3). This produced five distinct areas of greater patient activation (Figure 1), including the left precentral gyrus (BA 6), the left middle temporal gyrus (BA 37), the left postcentral gyrus (BA 2, 43), the left cingulate gyrus (BA 24), and the left parahippocampal gyrus (BA 19). All studies included in this contrast accounted for group performance differences.

**Episodic Retrieval**

**Healthy comparison subjects.** Nine studies reported retrieval results for healthy subjects, resulting in 108 foci. Table S4 in the online supplement lists the 11 distinct brain regions activated. These included the left and right frontal gyri (BA 6, 9, 46), the right middle (BA 46) and medial frontal gyri (BA 6), the left superior frontal gyrus (BA 6), the left inferior temporal gyrus (BA 20), the left and right superior parietal gyri (BA 7), the left precuneus (BA 7, 31), the left supramarginal gyrus (BA 40), the left and right middle occipital gyri (BA 18), the right insula (BA 13), and the thalamus bilaterally.

**Schizophrenia patients.** Retrieval results were reported for patients in 11 studies, for a total of 111 foci (see Table S4 in the online supplement). Similar to healthy comparison subjects, patients activated the left inferior (BA 6, 9), right medial (BA 6, 11), and right middle (BA 9, 10) frontal gyri, the right superior parietal gyrus (BA 7), the left and right middle occipital gyri (BA 18), and the right thalamus. Patients showed additional areas of activation in the left middle frontal gyrus (BA 6, 46), the left middle temporal gyrus (BA 21), the left fusiform gyrus (BA 37), the left inferior parietal gyrus (BA 40), the left superior occipital gyrus (BA 19), and the cerebellum bilaterally.

**Comparison subjects > schizophrenia patients.** Ten studies contrasted activity groups during retrieval, resulting in 76 foci (Table 4). As seen in Figure 3, the most extensive differences were in the left inferior frontal gyrus (BA 45, 46), followed by differences in the left precentral (BA 6) and middle frontal gyrus (BA 8), the right anterior cingulate gyrus (BA 24), the left middle temporal gyrus (BA 21), the right cuneus (BA 17), the thalamus bilaterally, the right posterior cingulate gyrus (BA 31), and the cerebellum bilaterally.

Only seven studies (63 foci) controlled for group performance differences. When the ALE was limited to these studies, schizophrenia patients continued to have reduced activity in left inferior (BA 13, 46) and middle frontal gyrus (BA 8), the right anterior cingulate gyrus (BA 24), the thalamus bilaterally, the right cuneus, and the cerebellum bilaterally (see Table S5 in the online supplement). However, previously observed group differences in the left precentral gyrus (BA 6), the left middle temporal gyrus (BA 21), and the right posterior cingulate gyrus (BA 31) were no longer present.

**Schizophrenia patients > comparison subjects.** This inverse contrast was examined in six studies, resulting in 26 foci demonstrating greater patient than comparison subject activation during episodic retrieval (Table 4). As illustrated in Figure 3, patients had greater activation in the left precentral gyrus (BA 4), followed by right hemisphere differences in the medial frontal gyrus (BA 10), the middle frontal gyrus (BA 11), the middle temporal gyrus (BA 21), the right thalamus, and the right parahippocampal gyrus (BA 30). When ALE was limited to the four studies (21 foci) that controlled for performance differences (see Table S5 in the online supplement), patients continued to show greater activity than comparison subjects in the left precentral gyrus (BA 4), the right medial frontal gyrus (BA 11),
the right thalamus, and the right parahippocampal gyrus. There were no longer group differences in the right medial frontal (BA 10) and the medial temporal (BA 21) gyrus.

**Discussion**

This quantitative meta-analysis of episodic memory functional imaging studies, with a combined sample of 123 patients with schizophrenia and 137 healthy comparison subjects, found prominent deficits in the prefrontal cortex in patients. During encoding, these deficits were in the left frontopolar (BA 10, 32), ventrolateral (BA 45), and dorsolateral (BA 46) prefrontal cortex. During retrieval, the largest effects were also in the left ventrolateral and dorsolateral prefrontal cortex. When patients were provided with semantic encoding strategies, dorsolateral prefrontal cortex deficits remained, but activation of the ventrolateral prefrontal cortex was no longer reduced. This ventrolateral prefrontal cortex sparing is consistent with previous univariate (27, 61, 67–70) and meta-analytic studies (71), which suggests that the ventrolateral prefrontal cortex may compensate for reduced dorsolateral prefrontal cortex function during working memory and episodic encoding (21, 72, 73). In contrast, there was no evidence of reduced hippocampal or surrounding medial temporal lobe activation in patients versus comparison subjects during encoding or retrieval. The only group difference in the medial temporal lobe was a relative increase in activation in patients in the parahippocampal gyrus during encoding and retrieval. This prominent prefrontal dysfunction was not secondary to unequal performance, as prefrontal cortex deficits remained when studies that did not control for group performance differences were eliminated.

Patient dysfunction during encoding was relatively circumscribed, including portions of the prefrontal cortex and a default mode network (74) previously associated with increased task-related deactivation in schizophrenia.
across a wide array of behavioral paradigms (75, 76). Frontal lobe dysfunction was localized to the frontopolar, ventrolateral, and dorsolateral prefrontal cortex. These three regions are associated with discrete working memory and episodic encoding functions. The frontopolar prefrontal cortex provides for selection and processing of subgoals during working memory (77, 78); the ventrolateral prefrontal cortex is involved with semantic processing and working memory maintenance (79) and binding of items with their context during working memory and episodic encoding (80); and the dorsolateral prefrontal cortex is involved with active working memory maintenance and manipulation (67, 81) and with processing relationships between items during encoding (82, 83). These functional deficits suggest that patients have difficulty selecting and maintaining rules to process items in their context and in relation to each other to facilitate encoding. If rules are provided, schizophrenia patients appear capable of ventrolateral prefrontal cortex-mediated item-specific processing but remain unable to recruit the dorsolateral prefrontal cortex to establish more interactive relational memory representations, leading to severe deficits in relational memory (21).

Patient deficits were more distributed during retrieval, even after group performance differences were eliminated. Impairments were noted in a frontocortical-cerebellar-thalamic network previously described by Andreasen and colleagues (33, 37) as creating a condition of “cognitive dysmetria” in which patients have trouble coordinating sensorimotor and mental processes. However, cognitive dysmetria was formulated to extend beyond episodic retrieval, and our finding that these distributed regions were not impaired during encoding suggests that cognitive dysmetria cannot uniquely explain the pattern of our findings.
On the other hand, evidence is accumulating that many components of this distributed network mediate specific cognitive functions that are important for successful episodic retrieval. The dorsolateral prefrontal cortex is associated with postretrieval monitoring (84, 85), the anterior cingulate gyrus with error or conflict detection (86), the thalamus with attention and working memory (87), and the cerebellum with working memory and mental flexibility (88). These combined functional deficits suggest a scenario in which schizophrenia patients have difficulty monitoring their response output and detecting errors in order to flexibly adjust signal-detection thresholds to optimize sensitivity to targets while avoiding nontargets.

The aforementioned regions serve functions beyond episodic memory and are impaired in schizophrenia during other cognitive and emotional paradigms. The dorsolateral prefrontal cortex is broadly implicated in cognitive control mechanisms that allow information processing and behavior to vary adaptively from moment to moment, depending on current goals (89). Our ALE findings may reflect a more general deficit in control mechanisms such as context maintenance (90). Likewise, the thalamus is a central relay station that gates and filters sensory input to the cortex (91), and thalamic dysfunction may reflect a fundamental deficit in sensory integration. Because ALE combines disparate studies, our analysis is not sufficiently constrained to establish functional specificity of these memory deficits. Establishing this level of specificity would require a focused effort, such as the Cognitive Neuroscience Treatment Research to Improve Cognition in Schizophrenia (CNTRICS) initiative (92), to translate cognitive neuroscience tasks that are designed to parse these complex and overlapping functions to the study of schizophrenia.

The only group difference in the medial temporal lobe was increased activation in the parahippocampal gyrus in patients during encoding and retrieval. Overactivation in this and other regions (sensorimotor, middle cingulate gyrus, and middle temporal gyrus) in patients may reflect inefficient, compensatory brain activity as extraneous task-related activation can also be seen at early stages of learning before an optimal cognitive strategy has been reached (93), and during reorganization following acute brain injury (94). The parahippocampal gyrus is also associated with familiarity-based episodic retrieval (9), and excess activity in this region may reflect patients’ overreliance on familiarity-based retrieval because of a specific recollection deficit (95). Unlike the previous ALE study (22), we did not find reduced hippocampal activation in schizophrenia, which may have resulted from our exclusion of region-of-interest studies to preserve the validity of the ALE method. The absence of hippocampal findings on the whole-brain level may have reflected increased susceptibility of small regions to smoothing artifact, although there were still no differences when the smoothing kernel was reduced to 6 mm and the ALEs repeated (data available on request). The absence of hippocampal findings may also reflect minimal relational binding demands (96, 97), as most included studies employed overlearned word stimuli. As more studies are performed that contrast relational versus item-specific encoding and retrieval, it will be interesting to see if medial temporal lobe differences can be detected on a meta-analytic level.

Several caveats must be considered when interpreting the results of this meta-analysis. First, in light of the limited number of articles meeting the study criteria, it was necessary to combine studies with disparate encoding and retrieval conditions and varying stimulus characteristics. This has the advantage of revealing the most robust and replicable task effects and group differences across memory paradigms, but the disadvantage of limiting our ability to ascribe specific brain regions to discrete memory functions to the study of schizophrenia.

On the other hand, evidence is accumulating that many components of this distributed network mediate specific cognitive functions that are important for successful episodic retrieval. The dorsolateral prefrontal cortex is associated with postretrieval monitoring (84, 85), the anterior cingulate gyrus with error or conflict detection (86), the thalamus with attention and working memory (87), and the cerebellum with working memory and mental flexibility (88). These combined functional deficits suggest a scenario in which schizophrenia patients have difficulty monitoring their response output and detecting errors in order to flexibly adjust signal-detection thresholds to optimize sensitivity to targets while avoiding nontargets.

The aforementioned regions serve functions beyond episodic memory and are impaired in schizophrenia during other cognitive and emotional paradigms. The dorsolateral prefrontal cortex is broadly implicated in cognitive control mechanisms that allow information processing and behavior to vary adaptively from moment to moment, depending on current goals (89). Our ALE findings may reflect a more general deficit in control mechanisms such as context maintenance (90). Likewise, the thalamus is a central relay station that gates and filters sensory input to the cortex (91), and thalamic dysfunction may reflect a fundamental deficit in sensory integration. Because ALE combines disparate studies, our analysis is not sufficiently constrained to establish functional specificity of these memory deficits. Establishing this level of specificity would require a focused effort, such as the Cognitive Neuroscience Treatment Research to Improve Cognition in Schizophrenia (CNTRICS) initiative (92), to translate cognitive neuroscience tasks that are designed to parse these complex and overlapping functions to the study of schizophrenia.

The only group difference in the medial temporal lobe was increased activation in the parahippocampal gyrus in patients during encoding and retrieval. Overactivation in this and other regions (sensorimotor, middle cingulate gyrus, and middle temporal gyrus) in patients may reflect inefficient, compensatory brain activity as extraneous task-related activation can also be seen at early stages of learning before an optimal cognitive strategy has been reached (93), and during reorganization following acute brain injury (94). The parahippocampal gyrus is also associated with familiarity-based episodic retrieval (9), and excess activity in this region may reflect patients’ overreliance on familiarity-based retrieval because of a specific recollection deficit (95). Unlike the previous ALE study (22), we did not find reduced hippocampal activation in schizophrenia, which may have resulted from our exclusion of region-of-interest studies to preserve the validity of the ALE method. The absence of hippocampal findings on the whole-brain level may have reflected increased susceptibility of small regions to smoothing artifact, although there were still no differences when the smoothing kernel was reduced to 6 mm and the ALEs repeated (data available on request). The absence of hippocampal findings may also reflect minimal relational binding demands (96, 97), as most included studies employed overlearned word stimuli. As more studies are performed that contrast relational versus item-specific encoding and retrieval, it will be interesting to see if medial temporal lobe differences can be detected on a meta-analytic level.

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processes. With a larger group of studies to choose from, it would be informative to segregate ALE analyses based on encoding condition (e.g., item-specific versus relational), stimulus modality (e.g., verbal, nonverbal), and retrieval task (e.g., recall versus recognition, cued versus uncued, item-specific versus relational). Second, the ALE method does not account for differences in sample size across included studies. This can be a strength in that it reveals the central tendency of the data, but a limitation if a study with a small sample and large effects that may not replicate is included and unduly influences overall results. Fortunately, the majority of studies had relatively equal sample sizes. Finally, all but two studies examined patients while they were receiving antipsychotic medication, which raises the question of drug effects. However, a qualitative examination of the two studies of unmedicated patients, both retrieval studies (33, 37), revealed the same pattern of reduced patient activation in prefrontal, cingulate, thalamic, and cerebellar regions that was seen in the studies of medicated patients. This apparent lack of medication effects is consistent with several studies of unmedicated patients (54, 69) that documented reduced prefrontal activation in patients that was not restored by antipsychotic treatment (98).

In sum, the results of this study provide strong support for the conclusion that episodic memory impairments in schizophrenia during encoding and retrieval are related to a reduction in memory control mechanisms implemented by the anterior, ventrolateral, and dorsolateral prefrontal cortex. These results suggest that behavioral interventions developed forremediating memory deficits in patients with frontal lobe damage (99) may also be applicable to schizophrenia. Use of pharmaco-fMRI (100, 101) to identify compounds that improve prefrontal function (102) may also lead to new medications that improve memory and daily functioning in individuals with schizophrenia.
Received Sept. 2, 2008; revision received Jan. 22, 2009; accepted Feb. 17, 2009 (doi: 10.1176/appi.ajp.2009.08091307). From the Department of Psychiatry and Imaging Research Center, University of California (UC) Davis, Sacramento; Research Imaging Center, University of Texas Health Science Center at San Antonio; Department of Psychology and Dynamic Memory Lab, UC Davis, Davis; Department of Psychology, UC Berkeley; Department of Psychiatry, University of Texas Health Science Center at San Antonio. Address correspondence and reprint requests to Dr. Ragland, UC Davis Imaging Research Center, 4701 X St., Sacramento, CA 95817; jdragland@ucdavis.edu (e-mail).

All authors report no competing interests.

Dr. Ragland was supported by NIH grant MH059883 (principal investigator, Cameron S. Carter) and a Robert Wood Johnson Foundation award. Dr. Laird and Ms. Gonzales were supported by the Human Brain Project of NIMH (R01-MH074457-01A1; principal investigator, Peter T. Fox). Dr. Ranganath was supported by NIMH grant MH068721. Dr. Blumenfeld was supported by a Ruth L. Kirschstein National Research Service Award from NIMH (F31MH 79776).

The authors thank Drs. Cameron S. Carter and Andrew Yonelinas for helpful comments on earlier versions of the manuscript.

References


8. Scoville WB, Milner B: Loss of recent memory after bilateral hippocampal lesions. J Neurol Neurosurg Psychiatry 1952; 17: 11–21


36. Cairo TA, Woodward TS, Nigan ET: Decreased encoding efficiency in schizophrenia. Biol Psychiatry 2006; 59:740–746


44. Heinze S, Sartory G, Muller BW, de Greiff A, Forsting M, Juptner M: Neural activation during successful and unsuccessful verbal learning in schizophrenia. Schizophr Res 2006; 83:121–130


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82. Blumenfeld RS, Ranganath C: Dorsolateral prefrontal cortex promotes long-term memory formation through its role in working memory organization. J Neurosci 2006; 26:916–925


85. Rugg MD, Henson RN, Robb WG: Neural correlates of retrieval processing in the prefrontal cortex during recognition and exclusion tasks. Neuropsychologia 2003; 41:40–52


90. Cohen JD, Servan-Schreiber D: Context, cortex, and dopamine: a connectionist approach to behavior and biology in schizophrenia. Psychol Rev 1992; 99:45–77


102. Gray JA, Roth BL: Molecular targets for treating cognitive dysfunction in schizophrenia. Schizophr Bull 2007; 33:1100–1119