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Working Memory in Unaffected Relatives of Patients with Schizophrenia: A Meta-Analysis of Functional Magnetic Resonance Imaging Studies

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Working memory deficits, a core cognitive feature of schizophrenia may arise from dysfunction in the frontal and parietal cortices. Numerous studies have also found abnormal neural activation during working memory tasks in patients' unaffected relatives. The aim of this study was to systematically identify and anatomically localize the evidence for those activation differences across all eligible studies. Fifteen functional magnetic resonance imaging (fMRI) manuscripts, containing 16 samples of 289 unaffected relatives of patients with schizophrenia, and 358 healthy controls were identified that met our inclusion criteria: (1) used a working memory task; and (2) reported standard space coordinates. Activation likelihood estimation (ALE) identified convergence across studies. Compared to healthy controls, patients' unaffected relatives showed decreases in neural activation in the right middle frontal gyrus (BA9), as well as right inferior frontal gyrus (BA44). Increased activation was seen in relatives in the right frontopolar (BA10), left inferior parietal lobe (BA40), and thalamus bilaterally. These results suggest that the familial risk of schizophrenia is expressed in changes in neural activation in the unaffected relatives in the cortical-subcortical working memory network that includes, but is not restricted to the middle prefrontal cortex.

Key words: intermediate phenotype/endophenotype/functional magnetic resonance imaging (fMRI)/dorsolateral prefrontal cortex/meta-analyses

Introduction

Schizophrenia is a psychiatric illness characterized by reality distortion and cognitive deficits, and it is associated with a variety of genetic and environmental risk factors.[1] A recent multi-stage genome-wide association study of schizophrenia has suggested that 108 conservatively defined loci meet genome-wide significance.[2] It remains unclear nonetheless how these loci relate to the underlying neuropathology. One strategy to address this may be to focus on intermediate phenotypes, quantitative traits that lie on the causative pathway between genes and schizophrenia.[3,4]

Working memory is a cognitive workspace that serves as a temporary holding site for information to be held, processed, and manipulated for brief periods of time. The information is classified into verbal and nonverbal (visuospatial) components according to type.[5] Verbal working memory processes verbal information, eg, a sequence of numbers while visuospatial working memory relates to spatial and object information. Some evidence suggests that working memory deficits are present in both auditory and visual modalities in patients with schizophrenia[6] and relatively independent of clinical status,[7,8] and are stable through the course of the illness.[9] Other evidence suggests that patients with better working memory performance tend to experience lower positive and negative symptom levels[10,11] while therapeutic strategies to support working memory dysfunction may reduce psychotic load.[12] It is noteworthy that similar working memory deficits are also found in patients' unaffected relatives,[13–18] including the unaffected co-twins from monozygotic discordant pairs, linking those deficits specifically to the their expression of the familial risk for that disorder.[15] Bora et al[19] in a meta-analysis of studies that assessed cognitive functioning of patients' unaffected relatives found that verbal and nonverbal working memory were impaired with moderate effect sizes (0.32 and 0.35, respectively). Given that cognitive deficits could arise from a variety

of pathophysiological processes, in order to refine our evaluation of the credentials of working memory as an intermediate phenotype for schizophrenia, we wanted to map the brain activity linked to working memory performance in patients' unaffected relatives from all available fMRI studies.

One region of central interest to this meta-analysis is the dorsolateral prefrontal cortex (DLPFC), a region, ie, often structurally and functionally abnormal in both patients with schizophrenia and their unaffected relatives.[20–22] Structural and functional changes in the DLPFC are thought to have an effect on working memory performance in schizophrenia. For example, Wheeler et al[23] found that patients with thinner DLPFC bilaterally tended to achieve worse working memory scores. Another study found patients with greater aberrant increased neural activity of the right DLPFC cortex to display poorer levels of accuracy on a working memory task.[24] However, whether working memory-related abnormal DLPFC activation is core deficit or actually reflects failure elsewhere in the functional network remains unknown. Other work including a qualitative review has found evidence of abnormal working memory-related brain activation in patients' unaffected relatives in dorsal and ventral prefrontal cortex, the basal ganglia, and the cerebellum.[22,25–28]

The aim of this study was to systematically identify and then synthesize all the available evidence for altered brain activation from fMRI studies of working memory tasks in unaffected relatives of patients with schizophrenia using activation likelihood estimation (ALE) meta-analysis. ALE is a widely used quantitative method to evaluate the functional data from multiple studies using the same functional task (eg, working memory task) in different samples.[29,30] Since activation in the DLPFC in relatives may differ in some respects between verbal and visuospatial working memory,[28] and since our primary analysis would pool data from studies that used both types of working memory, we hypothesized that the ALE analysis would detect abnormal patterns of activation in the DLPFC in relatives compared to healthy controls as well as in other cortical and subcortical regions in a manner at least qualitatively similar to patients with schizophrenia.[31] Many of the published working memory studies used a region of interest (ROI) approach that could bias our results in favor of structures such as the prefrontal cortex and thalamus. Thus, we planned to repeat the meta-analysis a second time, but including only whole brain hypothesis-free studies, in order to test if the analysis method could affect the results. Furthermore, given the potential differences in the neural architecture underpinning different types of working memory,[32] further exploratory analyses were performed according to stimulus modality and working memory type. Finally, we conducted a jack-knife sensitivity analysis to test the reliability and robustness of the data.

Materials and Methods

Literature Search and Selection

We searched *Web of Science* using the keywords "working memory," "functional magnetic resonance imaging or fMRI," "schizophrenia," "siblings," "first degree relatives," "family study," "twin," "high risk," and "genetic risk" to collect English-language peer-reviewed studies that compared working memory in patients' unaffected relatives with a control group using fMRI. The end date for inclusion was December 2014. Reference lists were checked by hand and the authors contacted for key data such as coordinates maxima if not provided in their report.

Studies were excluded if (1) they failed to provide coordinates for the contrast between relatives of patients with schizophrenia and healthy controls, (2) they were review articles, comments, and case reports, (3) they included populations that had been previously reported, and (4) nonfirst-degree relatives and relatives experienced any kind of psychiatric disorder (eg, depressive disorder) and/or neurological disease, any psychopharmacological treatment and drug abuse. Among the 524 articles searched, 15 studies reporting results from 16 samples (1 study had 2 independent samples) met the inclusion criteria and were included in the meta-analyses. The flowchart of paper selection is provided in supplementary figure S1 in the Supplementary Materials.

Recorded Variables

We extracted the following information from each study: author; year; sample size; participant demographics (mean age, gender, familial relationships, years of education, IQ); stimulus type (letter, shape, faces, etc.), experimental design and type of working memory task; field strength; and cluster coordinates for activation associated with working memory tasks compared to a control condition or resting baseline (Montreal Neurological Institute, or Talairach); and data analysis method (whole brain/ROI based/hybrid) (table 1 and supplementary table S1).

Meta-Analytic Procedure

Behavioral Performance Analysis. Response accuracy and reaction time are 2 indices of working memory performance. Although not the primary outcome from these functional imaging studies, we first evaluated working memory performance data collected during the functional tasks. Effect sizes were estimated by Cohen's *d* with corrections for small sample sizes.[46] When means and standard deviations of each group were provided, Cohen's *d* was calculated. If the studies did not report means and standard deviations, we estimated Cohen's *d* using reported *t*, *F* statistics, or the significance values. The overall effect size was computed by estimating a weighted average of individual effect size using a random

Table 1. The Input Characteristic of Each Study in Meta-Analysis

Study	Stimulus	Task Contrast	Control > Relatives	Control < Relatives	MRI Characteristics		Analysis
					Field Strength (Tesla)	Reference	
Verbal working memory							
Thermenos et al[33]	Letters	Auditory Q3A-CPT > vigilance task	✓	✓	1.5	Talairach	Hybrid
Brahmbhatt et al[25]	Letters	2-back > 0-back		✓	1.5	Talairach	Whole brain
Seidman et al[34]	Letters	Auditory Q3A-CPT > vigilance task		✓	1.5	Talairach	Hybrid
Meda et al[35]	Letters	Visual Sternberg, all loads: encoding > baseline; recognition > baseline	✓		3.0	MNI	Hybrid
Bakshi et al[36]	Letters	2-back > 0-back	✓		4.0	Talairach	Whole brain
Diwadkar et al[37]	Letters	2-back > 0-back	✓		4.0	MNI	Hybrid
de Leeuw et al[38]	Letters	Verbal Sternberg, all loads: encoding > baseline; recognition > baseline; retrieval > baseline		✓	3.0	MNI	Whole brain
Callicott et al[27]	Numbers	2-back > 0-back	✓	✓	1.5	Talairach	Whole brain
Callicott et al[27]	Numbers	2-back > 0-back	✓	✓	1.5	Talairach	Whole brain
Seidman et al[39]	Letters	2-back > 0-back		✓	1.5	Talairach	Hybrid
Karch et al[40]	Numbers	2-back > 0-back	✓	✓	3.0	Talairach	Whole brain
Whitfield-Gabrieli et al[41]	Letters	2-back > 0-back		✓	1.5	Talairach	Whole brain
Visuospatial working memory							
Keshavan et al[42]	Shapes	Ocular motor delayed response > visually guided saccade task	✓		3.0	Talairach	Whole brain
Brahmbhatt et al[25]	Faces	2-back > 0-back	✓	✓	1.5	Talairach	Whole brain
Rasetti et al[43]	Shapes	2-back > 0-back		✓	1.5	Talairach	Whole brain
Choi et al[44]	Shapes	Spatial delayed-response: encoding phrase > baseline; maintenance phrase > baseline; tetrieval phrase > baseline		✓	1.5	Talairach	Whole brain
Diwadkar et al[45]	Faces	Response type: correct > incorrect		✓	4	MNI	Whole brain

Note: MNI, Montreal Neurological Institute.

effects model. A 95% confidence interval (CI) was derived to access statistical significance. The *Q*-test of homogeneity[47] was used to test for variations in effect size across studies. Funnel plots for random effects were used to identify any publication bias, and a sample size dependent statistic was plotted on the *y*-axis and the effect size on the *x*-axis. An inverted symmetrical funnel indicates no publication bias.

Coordinated-Based Brain Activation Meta-Analytic Technique. The ALE procedure was implemented in GingerALE2.3.[29] Any activation foci coordinates not reported in Talairach space were transformed using Lancaster transformation (icbm2tal).[48] In order to calibrate for inter-subject variation in functional anatomy, rather than using a predefined full-width at half-maximum (FWHM) filter for smoothing, an algorithm was used to model the spatial uncertainty of each focus using an estimation of the inter-subject and inter-laboratory variability typically observed in neuroimaging experiments.[29] During the ALE calculation, based on the collection of peak coordinates from each study identified in the meta-analysis, ALE estimates the probability that at least one of the peaks lies within a voxel. This computation is performed at each voxel in the brain to produce an ALE map. The ALE maps were reported after correction for multiple comparisons using the false discovery rate (FDR) method at $q < 0.05$ and cluster size ≧ 200 mm.[3]

Exploratory Analyses

Effects of Data Analysis Method. By focusing on regions with greater statistical effects, the power to detect or replicate genetic effects is vastly increased. Studies that investigated the familial and genetic effects of schizophrenia liability have often adopted a ROI or hybrid whole brain and ROI (either small volume correction or a reduced threshold for a priori regions) to test research hypotheses.[49] Unlike previous ALE meta-analyses that only included whole brain voxel-wise analyses only, we chose to conduct 2 separate analyses. Firstly we included both ROI and whole brain voxel-wise studies leading to 15 studies of 16 samples, while in the second analysis, only data from the whole brain studies (10 studies of 11 samples) were included. By conducting 2 separate analyses, we hoped to ascertain whether the method of interrogating the data affected the results.

Effects of Working Memory Type. There is evidence that the neural networks underpinning different types of working memory, eg, verbal and nonverbal, may differ. In light of this, we subdivided our analyses into verbal (11 studies of 12 samples) and visuospatial (5 studies of 5 samples) groups according to the experimental materials deployed.

N-back Working Memory Paradigm. Among the experimental paradigms used in functional neuroimaging studies of working memory, the most popular is the n-back task, in which subjects are asked to monitor the identity or location of a series of verbal or nonverbal stimuli and to indicate when the currently presented stimulus is the same as the one presented n trials previously. Previous work[32,50] have suggested that n-back is a robust means of identifying WM differences between patients with schizophrenia and healthy comparison subjects. In the current study, there were 8 studies (9 samples) that used versions of the n-back paradigm, a secondary analysis including studies using n-back paradigm only was performed.

Sensitivity Analysis

In order to test for study heterogeneity we conducted a jack-knife sensitivity analysis. This method tests/assumes that those brain regions where the jackknife sensitivity analysis demonstrates significant difference are more replicable and robust.[51,52]

Results

Characteristics of Selected Studies

Fifteen studies of 16 samples that contained 289 unaffected first-degree relatives (139 males/150 females) and 358 healthy controls (155 males/203 females) were included (table 1 and supplementary table S1). The mean age of patients' unaffected relatives ranged from 13.3 to 50.8 years and that of healthy controls from 12.5 to 40.5. All the studies recruited age and gender-matched groups of healthy control subjects. The mean intelligence quotient (IQ) ranged from 92.1 to 108.4 in patients' unaffected relatives. Among the selected studies, 10, 4, and 3 samples were scanned at 1.5, 3, and 4 Tesla, respectively. Twelve samples (7 samples processed using whole brain voxel wise analysis) and 5 samples (5 samples using whole brain voxel wise analysis) were categorized as verbal working memory and visuospatial working memory experiments, respectively.

Working Memory Performance Inside MRI Scanner

Figure 1 shows the effect sizes for working memory response accuracy and reaction time between unaffected relatives and healthy controls. Mean effect size for accuracy was low (Cohen $d = 0.32$), 95% CI [0.15–0.50], $P < 0.01$, while study heterogeneity was not significant, $Q(13) = 6.14$, $P > 0.05$. A sensitivity analysis showed that after removing outliners, overall effect size range from $d = 0.28$, 95% CI [0.12–0.47], to $d = 0.36$, 95% CI [0.18–0.54]. The funnel plot indicated no publication bias.

For working memory reaction time, the mean effect size was low (Cohen $d = -0.28$), 95% CI [−0.48 to −0.09], $P < 0.01$ but heterogeneity between studies was significant

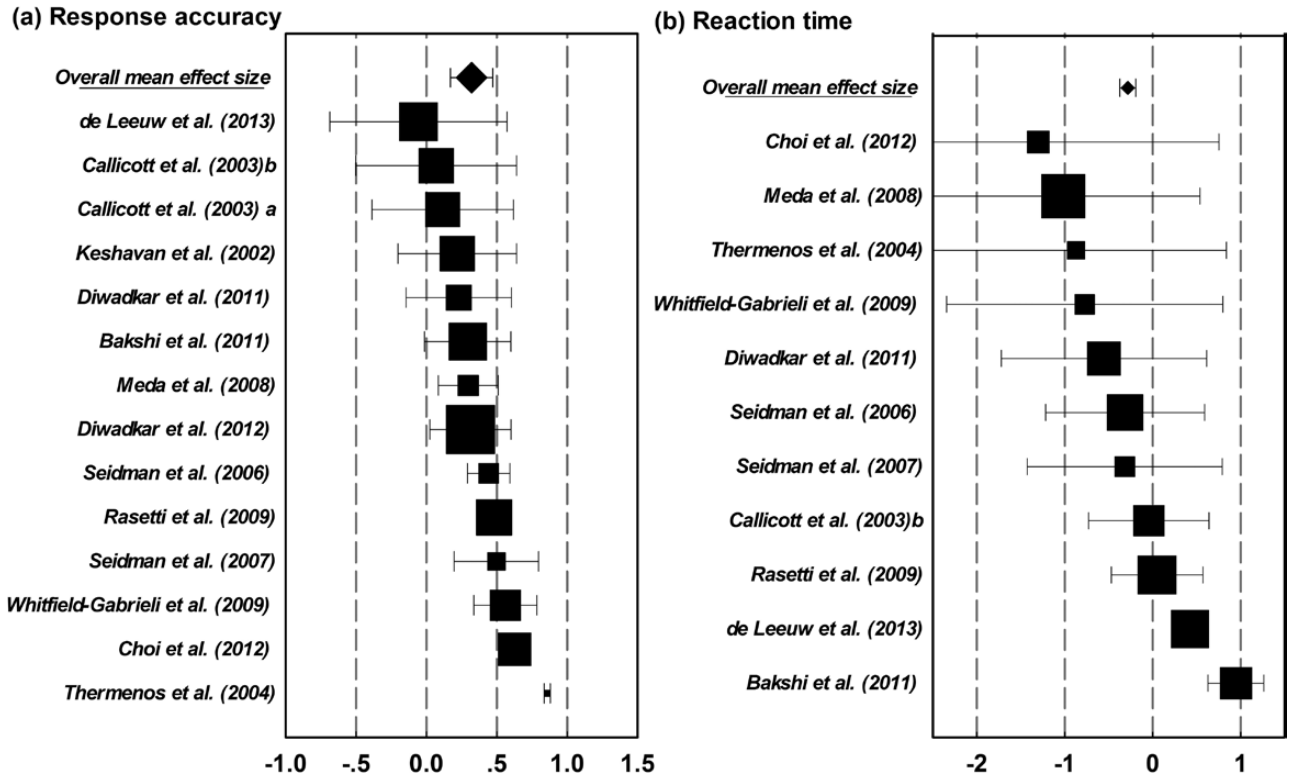

Fig. 1. Forest plot for working memory performance in the MRI scanner showing the overall average effect size and confidence interval (Cohen's *d*, displayed as a diamond, "◆") and individual effect sizes (Cohen's *d*, displayed as a rectangle "■"), 95% confidence intervals represented by horizontal lines. (a) Response accuracy. (b) Reaction time. Patients' unaffected relatives demonstrated less accurate and engaged longer response times on the working memory tasks. The positive and negative effect size represents the less accurate rates and longer response time in patients' unaffected relatives contrast with healthy controls, respectively.

$Q(10) = 36.99$, $P < 0.01$. A sensitivity analysis showed that after removing outliners, the overall effect size range from $d = -0.41$, 95% CI [−0.62 to −0.21], to $d = -0.21$, 95% CI [−0.41 to −0.01]. The funnel plot indicated no publication bias.

Working Memory-Related Brain Activation Difference

All Studies Including ROI Primary Studies. Compared to healthy controls, patients' unaffected relatives showed an increased neural activity in the right middle frontal gyrus [Brodmann area (BA) 10], left inferior parietal lobule (BA40), and bilateral thalamus. Compared with healthy controls, reduced activation in relatives was found in the right middle frontal gyrus (BA9) and the right inferior frontal gyrus (BA44). The peak coordinate of each region is displayed in figure 2 and table 2.

Whole Brain Studies Only. To exclude the effects of prior hypotheses and analytical method, we repeated the analysis restricted only to studies that adopted a whole brain voxel-wise approach (11 samples). Two clusters, 1 in the right middle frontal gyrus and 1 in the left inferior parietal lobule were associated with greater activation in relatives (table 2). Two clusters, 1 in the right middle and 1 in the right inferior frontal gyri were associated with reduced activation in unaffected relatives compared to controls.

Exploratory Analyses

Verbal Working Memory. Twelve samples reported on verbal working memory tasks. Compared to healthy controls, relatives showed greater activation in the right thalamus, right middle frontal gyrus (BA10), and right inferior parietal lobule (BA 40), and 2 clusters of reduced activation in the right middle (BA9) and right inferior frontal gyri (BA44) (supplementary figure S2 and table S2).

Visuospatial Working Memory. Five samples used visuospatial working memory tasks. Greater activation was seen in the relatives in the left superior temporal gyrus (BA22), the left middle frontal gyrus, the right inferior parietal lobule (BA40), and right precentral gyrus (BA6) (supplementary figure S2 and table S2). No areas of decreased activation were detected in relatives in contrast with healthy controls.

N-back. We restricted the analysis to the 8 studies (9 samples) that used versions of the n-back paradigm,

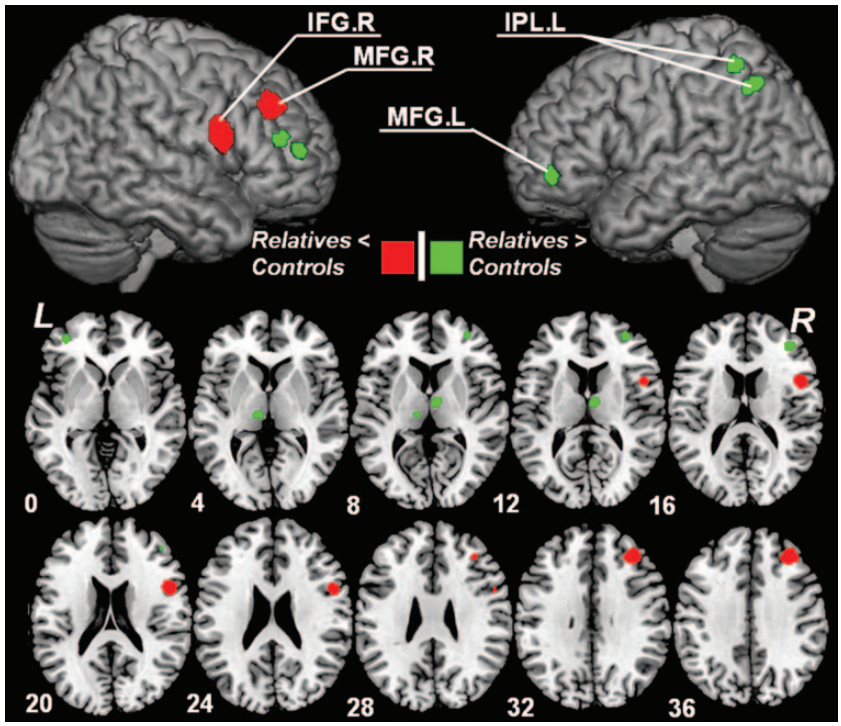

Fig. 2. Above-threshold brain activations for contrasts of healthy controls greater than relatives (red) and unaffected relatives greater than healthy controls (green). MFG: middle frontal gyrus; IFG: inferior frontal gyrus; IPL: inferior parietal lobule. L (R), left (right) hemisphere. Axial slices are presented in neurological convention with the corresponding Talairach *Z* coordinate.

Table 2. Brain Activity Patterns Demonstrating Group Differences for Working Memory Studies

Region	BA	Talairach Coordinates			ALE Value (10^{-2})	Cluster Size (mm^3)
		x	*y*	*z*		
All studies including ROI primary studies						
Controls > relatives						
Right middle frontal gyrus	9	36	36	34	3.3	1776
Right inferior frontal gyrus	44	52	10	18	3.1	1392
Controls < relatives						
Right middle frontal gyrus	10	32	50	10	1.5	472
Left frontal lobule		−36	46	−2	1.3	384
Right thalamus		4	−10	10	1.2	368
Left inferior parietal lobule	40	−36	−52	56	1.1	240
Right middle frontal gyrus	10	38	40	16	0.9	224
Left thalamus		−10	−20	4	0.9	216
Left inferior parietal lobule	40	−40	−60	44	0.9	216
Whole brain studies only						
Controls > relatives						
Right middle frontal gyrus	9	34	36	34	3.1	1528
Right inferior frontal gyrus	44	52	10	18	3.0	1360
Controls < relatives						
Right middle frontal gyrus	10	32	50	10	1.5	544
Left inferior parietal lobule	40	−40	−60	44	0.9	304

Note: BA, Brodmann area; ALE, activation likelihood estimation; Talairach coordinate for the maximum ALE value.

firstly including whole brain and ROI studies, then whole brain studies alone. We found evidence of increased activation in the unaffected relatives in the right middle frontal gyrus (BA8) and left inferior parietal lobule (BA40) irrespective of whether the ROI studies were included or not (supplementary table S3). Similarly, reduced activation was detected in the unaffected relatives in the left thalamus and in the superior frontal gyrus bilaterally, irrespective of whether the ROI studies were included or not.

Sensitivity Analyses

All of the jack-knife sensitivity analyses demonstrated decreased activations in the right middle frontal gyrus and 8 out of the 9 supported reduced activation in the right inferior frontal gyrus in unaffected relatives compared to healthy controls, suggesting that these results are highly reliable (supplementary table S4). All of the 12 studies showed increased brain activations in relatives compared to the controls in the right middle frontal gyrus and the left inferior parietal lobule. Eleven and ten jack-knife sensitivity analyses showed increased brain activation in the right and the left thalamus, respectively.

Discussion

We performed a meta-analysis after systematically identifying 15 studies reporting working memory-related brain activation in the unaffected relatives of patients with schizophrenia. Our results provide evidence for the hypothesis that first-degree relatives of patients with schizophrenia exhibit different activation patterns when engaged in working memory tasks. More specifically, relatives displayed less activation within the prefrontal cortex—in the right middle (BA9) and right inferior frontal gyri (BA44), supporting the idea that the prefrontal cortex is intimately linked to the familial risk for schizophrenia. To compensate the underlying working memory performance deficits, the relatives developed greater activation on frontopolar areas (BA10), the left inferior parietal lobule (BA40) and thalamus.

Findings of decreased activation in the right middle and right inferior frontal gyri are consistent with an earlier meta-analysis of executive function tasks in unaffected relatives.[53] It is thought that the middle frontal gyrus supports the central executive that may be critical for effective cognition and mnemonic strategy. The middle frontal and inferior frontal gyri contribute to central executive control, to strategic reorganization, and to the control of working memory.[54,55] Abnormal middle frontal gyrus activation could be linked to a failure to implement effective cognitive control and, eg, a failure to develop an effective mnemonic strategy in the unaffected relatives.[56,57] Bonner-Jackson et al[57] found that after manipulation of the levels-of-processing, ie, deep encoding, unaffected relatives improved their verbal working memory performance and increased neural activity of the right middle frontal gyrus. Encoding deficits may be one of the key factors impairing memory performance in patients with schizophrenia and their relatives[6,58,59] that underpin impaired memory performance.[60] Thus, our findings suggest that impaired working memory performance may be linked to abnormal middle and inferior frontal activation during working memory, perhaps reinforcing their status as a candidate endophenotype for schizophrenia.

In contrast, patients' unaffected relatives showed relatively greater activity in the frontopolar area (BA10) and the left inferior parietal lobule (BA40). It is possible that these regions are associated with a compensatory response and are recruited as alternative means to support task performance in a manner that has already been suggested in other studies.[31,61,62] With decreased DLPFC regulation of the distributed working memory network, relatives may perhaps need to deploy alternate neural resources to maintain task performance, eg, alternate mnemonic or performance monitoring facilities. The frontopolar area is an important substrate for organized behaviour, action planning, and the management of multiple goals linked to working memory.[63] The inferior parietal lobule plays a role in the retention of temporal information and attention shifting.[32] Activity in the left dorsal inferior parietal cortex is often seen in working memory tasks, especially when load and attention demands are high.[64–66] For example, Ravizza et al[64] found that the neural activity of the left inferior parietal lobule tended to be higher in the high-load condition in the N-back task. Our exploratory analyses of the n-back paradigm, whether we included the ROI studies or not (supplementary table S3) lead to similar results. The increased activation seen in these regions suggests that to manage the same working memory load (eg, 2-back), patients' unaffected relatives need additional or greater neuronal resources to possibly counter an underlying functional deficit in the middle and inferior frontal gyri.

We also found that relatives exhibited greater activation in the thalamus bilaterally in line with reports of increased basal perfusion of the thalamus in relatives[67] and possibly linked to thalamic volume reduction in relatives.[68–70] A meta-analysis of thalamic volume in schizophrenia found volume reductions with an effect size of $d = 0.68$.[71] Furthermore, thalamic dysconnectivity may be a key feature of schizophrenia.[72] We should perhaps remain cautious not to over interpret the thalamic findings however given that the activation differences were only found when the ROI studies were included. It is possible that in addition to a common working memory network that different brain regions support different types of working memory (verbal and visuospatial). Owen et al[32] conducted an ALE based quantitative meta-analysis and found that the thalamus was only activated for verbal but not visuospatial working memory tasks. Our exploratory analyses of working memory subtypes detected similar results (supplementary table S2). Alternatively, it is possible that the thalamic differences between unaffected relatives and controls are in fact more subtle than in other regions and that the removal of the ROI studies lead to a loss of power to detect those subtle between group differences. Our jack-knife sensitivity analysis partly supports this inference, as the thalamic brain activation differences were lost when one of 2 studies using the thalamus as an a priori ROI was excluded[33,34] (supplementary table S4). Future studies may need to consider reporting both ROI and whole brain voxel wise analyses to address this problem.

Some limitations should be considered when assessing the impact of these findings. Firstly, the sample size was

modest, but the study was still sufficiently powered to find reliable working memory-related brain activations. ALE has been conducted successfully with similar sample sizes before,[50,73] as the power of ALE depends on the consistency of activation in the individual studies rather than solely the number of studies available. Second, the meta-analysis for the working memory performance showed a low effect size, but it was still significant (figure 2) which means that performance differences between the relatives and healthy controls may be an important confounding factor that should be taken into account during the data analysis. However, among the 15 included studies, only one controlled for performance differences during data processing.[33] To exclude the potential difference between regressing out and un-regressing out, we excluded the coordinates regressing out the performance, but an implication for future study is the controlling of performance. Third, although the current model of ALE has many advantages and strengths in estimating the homogenous action across studies, currently it cannot weigh the difference between methods, eg, statistical threshold across studies employed. Fourth, this meta-analysis would benefit from being able to explore the effects of specific sample variables (eg, offspring), but the current sample size impeded doing this.

Conclusions

Our meta-analysis of fMRI studies comparing brain activations in unaffected relatives of patients with schizophrenia and controls identified aberrant activation patterns throughout working memory tasks. Relatives demonstrated less activation within the prefrontal cortex—in the right middle frontal gyrus (BA9) and the right inferior frontal cortex (BA44); more activation was detected in the frontopolar areas (BA10), left inferior parietal lobule (BA40), and thalamus. These activation patterns suggest that aberrations of brain function appear to be promising endophenotypes, and researchers should consider the entire network of regions involved in a given task when making inferences about the impact of genetic loading effects on neurocognitive function in schizophrenia in future studies.

Supplementary Material

Supplementary material is available at http://schizophreniabulletin.oxfordjournals.org.

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