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Imaging Genetic Liability to Schizophrenia: Systematic Review of fMRI Studies of Patients' Nonpsychotic Relatives

Angus W. MacDonald, III[1–3], Heidi W. Thermenos[4–6], Deanna M. Barch[7–9], and Larry J. Seidman[4–6]

[2]Department of Psychology; [3]Department of Psychiatry, University of Minnesota; [4]Department of Psychiatry, Harvard Medical School, Massachusetts Mental Health Center Public Psychiatry Division, Beth Israel Deaconess Medical Center; [5]Department of Psychiatry, Harvard Medical School, Massachusetts General Hospital; [6]MGH/MIT/HMS Athinoula A. Martinos Center for Functional and Structural Biomedical Imaging; [7]Department of Psychology; [8]Department of Psychiatry; [9]Department of Radiology, Washington University of St Louis

There is a growing literature on brain activity in the nonpsychotic first-degree relatives of patients with schizophrenia as measured using functional imaging. This systematic review examined 20 studies in 4 domains of cognition, including cognitive control (7 samples), working memory (5 samples), long-term memory (4 samples), and language (4 samples). While the literature was widely divergent, these studies did consistently find activation differences between patients' relatives and controls. The most consistent increases in activation within hemisphere were found in right ventral prefrontal cortex (PFC) and right parietal cortex. Abnormal activity, defined as significant increases or decreases in activation relative to controls irrespective of hemisphere, was found in about two-thirds of contrasts in the cerebellum, dorsal prefrontal, lateral temporal, and parietal cortices, and thalamus, with basal ganglia and ventral PFC showing abnormalities in approximately half of those contrasts. Anterior cingulate was generally spared in patients' relatives. The diversity of findings in studies of patients' relatives may derive from differences between the cognitive demands across studies. We identify avenues for building a more accurate and cumulative literature, including symmetrical inclusion criteria for relatives and controls, recording in-scanner responses, using both a priori and whole-brain tests, explicitly reporting threshold values, reporting main effects of task, reporting effect sizes, and quantifying the risk of false negatives. While functional imaging in the relatives of schizophrenia patients remains a promising methodology for understanding the impact of the unexpressed genetic liability to schizophrenia, no single region or mechanism of abnormalities has yet emerged.

Key words: schizophrenia/neuroimaging/fMRI/relatives/family study/cognitive control/working memory/memory/language/review

Introduction

The liability to schizophrenia is highly heritable, as shown through the patterns of risk in twins and other family members. However, robust susceptibility genes for schizophrenia have not yet been identified, due in part to its complicated mode of inheritance.[1,2] The identification of biological markers that are presumably more proximal to the activity of genes contributing to schizophrenia etiology has been an elusive goal in psychiatric genetic research. However, such markers remain much sought after because they have the potential to improve the ability of genetic studies to detect risk genes.[3–5]

This goal has led to a strong interest in the study of first-degree relatives of persons with schizophrenia, who offer a complementary perspective from which to search for biological markers associated with genetic risk (endophenotypes).[3,6,7] First-degree relatives harbor some of the risk genes for schizophrenia[8] as they are at 10-fold increased risk to develop the disease and share about half of their genes with their ill relatives. Relatives are also relatively free of biological changes that may be secondary effects of the acute psychotic state (ie, effects of medications, substance use, and institutionalization on physiology). This increased interest in the search for heritable biological markers in relatives initially led to the study of brain structure and cognitive functioning in relatives.[9] To date, this strategy has yielded only a few biological markers robustly associated with the genetic liability. For example, a recent meta-analysis showed that smaller hippocampal volume is characteristic of both first-degree relatives and persons with schizophrenia compared with controls,[10] suggesting that it is a biological vulnerability indicator. Qualitative reviews[11–13] and

[1]To whom correspondence should be addressed; Department of Psychology, University of Minnesota, N218 Elliott Hall, 75 East River Road, Minneapolis, MN 55455; tel: 612-624-3813; fax: 612-625-6668, e-mail: angus@umn.edu.

meta-analyses[14–17] have also established that a wide variety of cognitive deficits are present in nonpsychotic relatives of persons with schizophrenia. These deficits in relatives are similar to, but milder than, those found in patients. However, deficits in many, if not all, of these cognitive functions could arise from a number of different neurobiological disturbances. Thus, an important challenge for the field is to refine the cognitive phenotypes used in behavioral and clinical studies in order to better understand the functional neuroanatomy of the unexpressed genetic liability to schizophrenia.

Toward this end, there has been a sharp increase over the past 5 years in the number of studies using functional imaging to measure brain activity in nonpsychotic relatives of persons with schizophrenia. These studies help to address a number of problems that limit the interpretability of brain function studies in patients that can lead to spurious findings. For example, schizophrenia impairs patients' attention and motivation, which can affect both task performance and brain activity.[18] Medication, high levels of nicotine use,[19,20] and substance abuse in patients affect both cognitive functioning and blood oxygen–dependent (BOLD) response physiology. The short half-lives of some of these substances can have inconsistent effects on physiology over the course of an experiment,[21] whereas their chronic use may alter long-term patterns of brain activity. Finally, unemployment, underemployment, and institutionalization in patients may have unforeseen effects on cognitive performance and the resulting physiology. In contrast to patients, relatives tend to have milder cognitive deficits, lower rates of substance use, unemployment, and other potentially confounding variables, making it easier to match them to controls[22] and to interpret functional imaging results.

The study of schizophrenia patients' nonpsychotic relatives' trait-like disturbances in functional neuroanatomy is several levels of analysis removed from the cellular and neurochemical causes of the disorder. Such studies do not provide definitive proof implicating one gene or neurotransmitter system over another. Instead, functional neuroanatomy is useful for determining which brain systems are likely to reflect the microbiological vulnerabilities associated with the diathesis. For example, a consistent signal implicating early perceptual processing regions, the thalamus, basal ganglia, hippocampus and medial temporal cortical structures, or the various regions of prefrontal cortex (PFC) all have different implications for how the genetic liability to schizophrenia may be expressed.

Functional imaging studies of patients' relatives have tapped a number of different cognitive domains and used many different tasks, experimental designs, and statistical methods. This project was undertaken to systematically evaluate and integrate this rich bounty. Our goal was to determine whether there existed consistent findings across studies that pointed to a reliable relationship between genetic liability and brain dysfunction and to address the following questions: Are there any brain regions that show the impact of genetic liability irrespective of the cognitive demands? What experimental approaches or reporting practices provide the clearest picture of biological markers associated with genetic risk for schizophrenia? To address these questions, the current report reviews the available studies that image the unexpressed genetic liability to schizophrenia to identify (1) common themes or consistencies across studies, (2) common problems or confounds that could be addressed in future studies, and (3) promising avenues for future work.

Review Methods

Studies were identified from PubMed through November, 2007, using SCHIZOPHRENIA crossed with RELATIVES or FAMILY STUDY and IMAGING or fMRI, through the bibliographies of identified studies and by directly contacting authors actively researching in this area. Twenty-two articles were found representing 23 nonindependent samples that were either published or were in the process of being published. Twenty imaging studies of schizophrenia patients' relatives (19 fMRI and 1 positron emission tomography [PET]) fell into 4 general domains—working memory, long-term memory, cognitive control, and language. There was only a single study in 3 domains (affect recognition,[23] early visual processing,[24] and olfactory processing[25]), which was thought to be too few to integrate. As a result, these will not be reviewed herein. Even within the 4 main categories, there was significant heterogeneity as far as tasks, analytic methods, and reporting practices. For this reason, it was deemed more important to highlight trends and potential concerns within this burgeoning field and less constructive to apply meta-analytic methods such as activation likelihood estimation.[26] Further, although our hope was that common themes would emerge, we felt that a focus on each subdomain would facilitate synthesis.

Studies were categorized and evaluated using 4 guidelines. First, based on a preliminary summary of the findings from these studies, we tracked 8 brain regions made up of discrete structures or clustered Brodmann areas (BAs): anterior cingulate, dorsal/dorsolateral prefrontal, ventral/ventrolateral prefrontal, parietal, and lateral temporal cortices, basal ganglia, thalamus, and cerebellum (see table 1 for regional definitions). Second, we made every effort to distinguish between regions where relatives and controls showed equal task-related activity and regions in which activity was not significantly elicited by the target cognitive task (the former were viewed as interpretable null findings, the latter were not viewed as informative about group differences). Specifically, regions in which there was statistically significant activity

Table 1. Functional Neuroimaging Family Studies of Cognitive Control

First Author, Year	Primary Task	Design	No. of Relatives[a]	No. of Controls	Relatives' Age	Perf.[b]	Brain Activity[c]								Other Brain Activity[h]
							ACC	DPFC	VPFC	Parietal	Temporal	BG	Thalamus	Cerebellum	
Raemaekers et al (2006)[27]	Antisaccade	Event	16s	16	33.9*	=[d]	Ø	=RL	Ø	=RL	Ø	↓RL	Ø	Ø	=R 6 =RL 17/18
Becker et al (2008)[28]	Stroop	Event	17u	17	33.3*	=	=*RL*	↑*R* ↓*L*	↑R, =L	↑L	Ø	Ø	Ø	Ø	
Thermenos et al (2004)[29]	Q3A-CPT	Block	12u	12	35.5*	Con > Rel	↑RL	↑RL	=RL	↑RL	↓R, =L	Ø	↑RL	Ø	↓R hippocampus =RL 18/19
Seidman et al (2007)[30]	Q3A-CPT	Block	12u	13	34.8*	=	?	Ø[e]	Ø[e]	?	?	?	↑R	?	
Delawalla et al (2007)[31]	AX-CPT	Block	30s	92	21.3*	Con > Rel	Ø	↑RL, ↓R[f]	↑RL	↑R	↑R	↑R	↑L	↑R	↑RL 6, ↑R 13, =L 13
MacDonald et al (2006)[32]	POP	Event	21u	20	33.2*	=[d]	=RL	↓R, ↑L[g]	↓L	↑RL	↑RL	=RL	=R	↓RL	=R hippocampus =RL 6 ↑RL 17/18
Vink et al (2006)[33]	Stop signal	Event	15s	15	35.0*	=	=	Ø	Ø	Ø	Ø	↓*R*	↑*RL*	Ø	=R 13
Summary	↑ ↓ =						1R,1L 3R,3L	4R,4L 2R,1L 1R,1L	2R,1L 1L 1R,2L	3R,3L 1R,2L	2R,1L 1R 1L	1R 2R,1L 1R,1L	3R,3L 1R	1R 1R,1L	

[a]Relative status: s, siblings; u, unspecified or heterogeneous relatives.
[b]Perf., performance results; Rel, relatives; Con, controls; "=," no statistically significant differences between groups in accuracy; ?, no data presented.
[c]Brain activity: ACC, anterior cingulate cortex, to include Brodmann area (BA) 24/32; DPFC, dorsal prefrontal cortex, to include BA 8/9/10/46; VPFC, ventral prefrontal cortex, to include BA 44/45/47; parietal to include BA 7/39/40; temporal to include BA 20/21/22/37/38/41/42; BG, basal ganglia, to include striatum, caudate, and globus pallidus; R, right hemisphere; L, left hemisphere; M, medial; ↑, greater activity in relatives; ↓, lower activity in relatives; "=," no between-group differences; Ø, region in which there was no significant task-elicited activity reported in either the sample of controls and/or the combined "supergroup" sample of controls and relatives; ?, region in which significant target task-elicited activity in the control or supergroup samples was not reported. Italics indicate findings that occur utilizing a liberal threshold value.
[d]Significant differences in performance were observed in reaction times (Rel > Con), but not accuracy, in these studies.
[e]Nonsignificant increases in relatives were observed in these regions, RL DPFC $d = 1.65$–1.83 and R VPFC $d = 1.43$.
[f]↑RL DPFC was observed as a main effect of group and ↓R DPFC was observed in the group × delay interaction.
[g]↓R DPFC observed following the cue to be maintained and ↑L DPFC following both the cue and the response.
[h]Numbers here indicate other BAs.
Asterisk indicates where the mean age of relatives was not meaningfully different from controls ($P > .10$).

in the control group alone or in the combined sample of all relatives and controls were defined as regions with the *potential* to be sensitive to group differences. Thus, the absence of a group difference in a region shown to be activated in the controls or the entire sample was treated as a null result. However, the absence of group difference in a region not shown to be activated in either the controls or the entire sample suggested that the study was uninformative about any potential difference in that region. Also regions where group differences were found were considered to be de facto sensitive to group differences. Deactivations associated with task performance were generally not reported in the source articles and while this is an important area for future research, there is little we can say about this now. Third, for each study, the demonstration of a group difference *anywhere* within a brain region took precedence over a finding of equal activity in another part of the structure. Fourth, where more than one group of relatives was reported in a single study, we selected the relatives group that was described as less symptomatic to incorporate into the table.

An important methodological caveat is that family studies such as those summarized herein are designed to provide insight into the unexpressed genetic liability to schizophrenia. They largely assume that common environmental influences are absent or minimal. However, family studies cannot disentangle the effects of shared genes from shared environmental influences, nor do they identify unique environmental influences on the unaffected relative. This issue can best be assessed with large twin samples or the piecemeal study of putative environmental risk factors or specific alleles.

Findings Across 4 Cognitive Domains

Cognitive Control Studies

Cognitive, or top-down, control occurs when internal goals are used to coordinate perception, cognition, and action.[34] As such, cognitive control is an executive function implemented in a variety of behavioral tasks. Tasks designed to target cognitive control processes frequently involve controlling attention, ignoring conflicting information, or resolving conflicting impulses. The first report of a differential deficit in schizophrenia was a reduction in the ability to resist distraction, one aspect of cognitive control.[35] Differential deficits in cognitive control have also been identified in the genetic liability to schizophrenia.[36,37] The results of functional imaging studies of cognitive control in the nonpsychotic relatives of schizophrenia patients are summarized in table 1.

A canonical example of an experimental task that requires cognitive control is the antisaccade task,[38] on which patients with schizophrenia and their relatives exhibit robust, well-replicated deficits.[39] To examine the neuroanatomical basis of cognitive control in the healthy relatives of schizophrenia patients, Raemaekers and colleagues[27] compared brain activity during the antisaccade task compared with the prosaccade task. In the prosaccade baseline control task, a small square appeared to one side of the central fixation and participants were instructed to move their gaze to the square as quickly as possible. This is a relatively automatic response to a new stimulus. The antisaccade task was the same except that participants were instructed to shift their gaze to the side opposite where the square appeared. This requires a higher degree of cognitive control. Performance between relatives and controls was matched for accuracy, although controls responded faster in both conditions. Voxelwise analyses did not reveal group differences. In a priori contrasts that used a small volume correction to evaluate the caudate body, controls showed more activity than patients' relatives. One complication in interpreting results of this study is that both the antisaccade (experimental) and prosaccade (control) conditions showed behavioral impairments of approximately the same magnitude (eg, d's = 0.50 for saccade latency). Subsequent analyses modeled activity for reaction times and correct trials, so the complication is not that poor performance may have led to differences in activity. Instead, the concern, not at all unique to this study, is that the subtraction did not isolate any cognitive process implicated in the unexpressed genetic liability to schizophrenia. Second, the importance of the caudate body is not clear, given that a higher threshold was used to evaluate activity in every other region of the brain.

Another task commonly used to evaluate cognitive control functions is the Stroop task.[40,41] Becker and colleagues[28] evaluated relatives' performance on a single-trial variant of the traditional Stroop task. Here participants saw 1 of 3 words (RED, GREEN, or BLUE) that appeared in one of those 3 colors. Participants were instructed to name the color of each stimulus. This is easier when both the word and color are the same or congruent, as in 70% of the trials, but requires a controlled response when the word and color are different or incongruent. Relatives and controls were equally accurate on the task; however, relatives were nonsignificantly slower on incongruent trials. In group comparisons, relatives showed increased activity in a region encompassing right dorsal and ventral PFC (BAs 10 and 47) and left parietal cortex (BA 40) and significantly decreased activity in left dorsal PFC (BA 9).

In addition to tasks that require the instantaneous implementation of cognitive control according to a stored rule, a number of tasks require the use of stored information that changes dynamically to guide performance. The first published functional imaging study of cognitive control in the nonpsychotic relatives of schizophrenia patients used a variant of the AX continuous performance test (AX-CPT) in which participants maintained the context of an auditory cue while being faced with distracting

auditory information.[29] This experimental task, called the Q3A-INT ("INT" for interference) because of the 3 sequential, interfering distractors (eg, "QraqA"), was compared with a baseline QA task, which also involved identifying the A as a target only if it followed a Q with no interfering letters. In both tasks, valid QA pairs occurred at approximately a 20% frequency. Performance differences were found on the Q3A but not the QA. When groups were analyzed together, the contrast of Q3A-INT to QA activated the cognitive control network encompassing dorsal and ventral PFC (BA 9/44/45/46), the anterior cingulate (BA 24/32), superior and inferior parietal lobules (BA 7/40), and thalamus, as well as hippocampal, lateral temporal, and occipital regions. When the 2 groups were compared, relatives showed greater activity in left dorsal PFC, anterior cingulate, and medial dorsal thalamus. After performance effects were controlled, the thalamus remained significant. In the primary analysis, the only region in which controls showed more activity than relatives was in the posterior hippocampus.

In an attempt to replicate the original finding in an independent sample of adult nonpsychotic relatives within a parametric design, Seidman et al. (ref 30) modified the original Q3A-INT design so that there were 3 versions differing on frequency of "q" and "a" distractors interposed between cue and probe stimuli. Moreover, the frequency (60% vs 100%) of potential Q3A-INT sequences was compared. Task performance was lower in relatives than controls (d = 0.52–0.60) but not significantly so. Analyses focused on contrasts in a priori regions, such that relatives again showed significantly more activity than controls in thalamus, but not the other areas previously reported (some of which showed subthreshold differences). There were no regions found wherein controls showed more activity than relatives. This is the only cognitive control paradigm that has been used in 2 independent samples with largely similar samples (both adult nonpsychotic relatives, mean age of approximately 40), yielding comparable results.

A similar task was used to evaluate a component of cognitive control known as context processing, which is the capacity to represent and maintain information needed to control behavior.[31] In the expectancy manipulation of the AX-CPT, participants identified the X as a target only if it followed an A, and in this task, most trials were A's followed by X. Thus, participants have to overcome their automatic tendency to make a target response when they see an X that follows an invalid cue, eg, a B. Indeed, relatives performed significantly worse on these BX trials when there was a delay of several seconds between the B cue and the X probe (d = 0.40), but not when the X followed the B after a very short delay. When comparing groups, the authors reported an interesting pattern of abnormal activity across the brain: first, the main effect of group indicated that siblings were more active across the cognitive control network, irrespective of the delay between the cue and probe. However, there was an interaction of group and delay in the dorsal PFC (BA 9/10), where controls exhibited more activation for the long delay, whereas relatives showed more activity for the short delay. One explanation for these findings is that controls were showing more preparatory activity in these regions following the cue, whereas relatives had more reactive activity when responding to the probe.

Yet another paradigm used in a study of patients' relatives directly addressed this difference between preparatory and reactive activity.[32] In the Preparing to Overcome a Prepotent Response task, a green or red square served as a cue to indicate whether to make an automatic or controlled response to the subsequent probe. After several seconds, a probe appeared on the left- or right-hand side of the screen. Following the green square, participants responded with the hand on the same side, and following the red square, participants responded with the opposite hand. The authors reported a group by condition interaction for reaction time (but not errors) such that red trials took comparatively longer for the patients' relatives (d = 0.58). Despite the task's dependence on activity across a very broad cognitive control network, differences in activity between relatives and controls were very modest. Following the red cue, controls showed more activity in right dorsal PFC (BA 6/8/9), whereas relatives showed more parietal (BA 40) and lateral temporal lobe (BA 21/37) activation. When making controlled responses, controls showed more activity in regions of left ventral PFC (BA 44/45), whereas here relatives showed more activity in left dorsal (BA 9) and frontopolar PFC (BA 10). These findings are consistent with a greater need for probe-related, reactive activity in patients' relatives.

Another perspective on the dynamic nature of cognitive control has been provided by use of the stop-signal task.[33] In the stop-signal task, the majority of trials required participants to respond with either a left or right button press when an X appeared to one side of the central fixation. On 20% of trials, the X was followed shortly by a signal, indicating that the response must be suppressed. The longer the delay between the appearance of the X and the stop signal, the harder it was to suppress the response.[42] Despite the fact that the experimenters titrated this delay to minimize behavioral differences across groups, patients' relatives tended to make more errors on the stop-signal trials. In a first, whole-brain exploratory analysis that contrasted blocks containing both go and stop trials to blocks containing just go trials, patients' relatives showed greater thalamic activity. In a second, confirmatory analysis evaluating the effect of the increasing likelihood of a stop trial, controls had greater striatal activity. Notice that this contrast does not address the implementation of top-down cognitive control (as one might see, eg, when evaluating activity on a stop trial), but it does highlight differences in the anticipation of a need for control.

Cognitive Control Summary. Cognitive control has been studied using a number of tasks and has begun to yield promising results, particularly for bilateral dorsal PFC, parietal cortex, and thalamus. Right dorsal PFC showed increased activation for relatives in 3 contrasts, equal activation in 1 and decreased activity in 2 others, whereas left dorsal PFC was increased in 3, equal in 1 and decreased in 1 more. When considering abnormalities irrespective of direction or laterality, dorsal PFC showed abnormalities in 82% of contrasts. Right and left parietal cortex showed increased activation for relatives in 3 contrasts and no differences in 1 and 2 contrasts, respectively. Considering abnormalities broadly, parietal cortex was impaired in 67% of contrasts. Thalamus showed increases in relatives in 3 right and 3 left locations, whereas it was not different in only 1 study. Thus, 86% of contrasts showed abnormalities in this region. Ventral PFC also showed suggestive evidence of impairments across studies. Qualitatively, a number of common threads emerged from tasks designed to evaluate cognitive control in the nonpsychotic relatives of patients with schizophrenia. Across a number of independent studies, anterior cingulate activity was intact in the patients' relatives. If there is a pattern associated with differences in directionality in dorsal PFC, one might observe that blocked design tasks have found hyperactivity, whereas event-related tasks have either found no differences or found a more nuanced profile. One possibility is that different phases of task response have different control-related demands. For example, the findings of MacDonald et al[32] and Delawalla et al[31] and respective colleagues have suggested that relatives show reduced activity when preparing a controlled response. Then, to overcome the lack of proactive control, they show greater activity when executing a controlled response. Interestingly, the behavioral data acquired during scanning in the cognitive control studies has yielded much more consistent evidence for behavioral impairments (often in the range of moderate effect sizes [ESs]) than found in studies of other cognitive domains reviewed below. At this point, it is not clear whether this reflects a truly greater deficit in cognitive control compared with other processes in relatives or whether the psychometric characteristics of the cognitive control tasks used have more discriminating power than in other domains, or more fine-grained analysis of behavior is possible in such studies.

Working Memory Studies

Working memory is generally defined as the process of actively maintaining and manipulating information for a short period of time and is involved in many cognitive tasks and day-to-day activities, such as reading a sentence, solving a math problem, or imagining an object's appearance from another perspective.[43] Meta-analytic studies demonstrate that working memory deficits are a core feature of schizophrenia, independent of the modality examined and the length of the delay period.[44] First-degree relatives of persons with schizophrenia also manifest deficits in working memory.[16,45–47] Functional neuroimaging studies of working memory in schizophrenia demonstrate a complex pattern involving regions of both hypo- and hyperactivation in the frontal lobe,[48] findings which appear to depend in part on working memory task performance.[49–51] The results of functional imaging studies of working memory in the nonpsychotic relatives of schizophrenia patients are summarized in table 2.

In the study of working memory in nonpsychotic relatives of individuals with schizophrenia, Keshavan and colleagues[55] compared brain activation in 4 child and adolescent offspring of patients with schizophrenia and 4 age- and sex-matched controls performing memory-guided and visually guided saccade tasks. The memory-guided saccade task required subjects to retain information about the spatial location of an item over a short interval, after which they were required to make an eye movement to the target location. The visually guided saccade task required subjects to perform an eye movement to the location of a visual cue and served as the subtractive, sensorimotor control task. Compared with controls, offspring showed reduced activation in the dorsal PFC bilaterally (BA 9/46), the right middle frontal cortex (BA 8), and the right inferior parietal cortex (BA 40), in the absence of group differences in task performance. For the purpose of our overview, we did not integrate the findings of this study with the other reports in this review as generalizability was limited by the sample size.

Callicott and colleagues[56] evaluated working memory functioning in 2 independent samples of 23 and 25 nonpsychotic siblings of people with schizophrenia compared with healthy controls. Here, subjects viewed visual stimuli (the numbers 1–4 appeared randomly every 1.8 s for 500 ms) at set locations on the points of a diamond-shaped box. This version of the n-back involved a spatial component such that instructions displayed above the diamond informed the subjects to recall the stimulus seen "N" previously (working memory load was varied from 0-back to 1-back to 2-back in the first study and from 0-back to 2-back in the second study and corresponded to delays of 0, 1.8, and 3.6 s for 0-, 1-, and 2-back stimuli, respectively). N-back task performance was similar across groups, although age was not. In both studies, siblings had significantly greater activity in the right dorsal PFC (BAs 9/10 and 46), bilateral ventral PFC (BAs 44/45 and 47), left parietal lobule (BA 40), and thalamus. Both studies also found relatively reduced activity in left dorsal PFC (BAs 10 and 8), precuneus (BA 7), lateral temporal cortices, thalamus, and cerebellum. Analysis of covariances used to examine effects of age, gender, and education on brain activity revealed no effects on between-group

Table 2. Functional Neuroimaging Family Studies of Working Memory

First Author, Year	Primary Task	Design	No. of Relatives	No. of Controls	Relatives' Age	Perf.	Brain Activity							Other Brain Activity (Brodmann area)
							ACC	DPFC	VPFC	Parietal	Temporal	BG	Thalamus	Cerebellum	
Callicott 2003a[56]	Visual n-back	Block	23s	18	34.4	=	↑*RL*	↑*R*↓*L*	↑*RL*	↑*R*↓↑*L*	↓↑*R*	?	↓*RL*	↓*RL*	↓*R hip.*, ↑*R 6*, ↓*L 31/30*, ↓*R 18*
Callicott 2003b[56]	Visual n-back	Block	25s	15	36.6	=	↓*RL*	↑*R*↓*L*	↑*RL*	↓*R*↓↑*L*	↓*RL*	?	↑*R*↓*L*	↓*RL*	↓*R hip.*, ↓*RL 6*, ↓↑*L 23/29/31*, ↓↑*R*↓*L 18/19/37*
Brahmbhatt et al (2006)[52]	Word and face n-back	Block	18s	72	20.7*	=	=RL	↓↑R[a]	Ø	↑L	=RL	↑R	=RL	↓↑RL[a]	=R 6, ↑L 1/2
Seidman et al (2006)[53]	Visual n-back	Block	21 o and s	24	19.9*	=	=RL	↑*R*	=RL	↑*R*	Ø	=RL	=RL	=RL	
Karlsgodt et al (2007)[54]	Letter Sternberg	Block	10t	13	51.9*	Con > Rel	?	=RL[b]	?	=RL[b]	?	?	?	?	=RL 18/19
Summary	↑						1R,1L	4R	2R,2L	2R,3L	1R	1R	1R	1R,1L	
	↓						1R,1L	1R,2L		1R,2L	2R,1L		1R,2L	3R,3L	
	=						2R,2L	1R,1L	1R,1L	1R,1L	1R,1L	1R,1L	2R,2L	1R,1L	

Note: o, offspring; t, twins; hip. hippocampus. Abbreviations are explained in the footnotes to table 1. Asterisk indicates where the mean age of relatives was not meaningfully different from controls ($P > .10$).
[a]Siblings showed hyperactivity on the word n-back and hypoactivity on the faces n-back in these regions.
[b]Performance-activity correlations in patients and relatives were in the opposite direction from controls.

BOLD differences in either study. This was a groundbreaking pattern of results that included an independent replication in a more restricted region of interest analysis in the second study. However, it should be noted that the statistical maps in these studies were thresholded at relatively liberal levels ($P < .01$ for study 1; $P < .05$ for study 2).

Brahmbhatt and colleagues[52] compared brain activation in 19 persons with schizophrenia, 18 of their siblings, and 72 controls performing another variant of the 2-back working memory task.[57] In this variant, stimuli (words or faces) appeared one at a time on a screen and subjects were told to push one button (target) any time they saw a stimulus that was the same as the stimulus they saw 2 trials back. If the stimulus was not the same as the one presented 2 trials back, they were told to push another button (nontarget). The n-back task was designed to asses the ability to code temporal order within the task by including repeat nontarget trials or "lures," whose prior presentation was not in the correct 2-back position (ie, was 1 trial or 3 trials prior). The sibling and control groups were comparable on demographic variables, Scale for the Assessment of Positive and Negative Symptoms scores and Vocabulary scores. Siblings and controls performed the task equally well, although siblings showed a trend toward worse performance than controls on repeated lure trials. For word stimuli, patients and their siblings showed increased right PFC activity (BA 10/46), and relatives showed bilateral hyperactivity in the cerebellum. For face stimuli, the opposite pattern was seen in the PFC and cerebellum, with *decreased* activation observed in patients and their siblings. These findings provided a partial replication of those of Callicott and colleagues in a younger sample that included both patients and siblings. The fact that the stimulus type significantly changed the direction of group differences was unexpected and must be replicated in further research.

The Harvard Adolescent High-Risk Study examined 21 nonpsychotic first-degree relatives ("high-risk" subjects, ages 13–28) and 24 comparable controls performing a 2-back task similar to that used in the Brahmbatt's report.[52] As with the previous study, performance of the in-scanner 2-back and simple vigilance tasks was similar across groups. A priori regions of interest in the PFC and superior parietal lobule (BA 7) defined from a meta-analysis of working memory studies[43] were selected for use in a region of interest analysis. Compared with controls, high-risk subjects showed significantly greater task-elicited activation in the right dorsal PFC (BA 46). Psychopathology, IQ, and in-scanner working memory performance did not account for group differences. Results were replicated when comparing high-risk subjects to a subsample of controls (n = 16) who had no parental psychiatric diagnoses. Of note is that the ES difference between groups was larger in the "diagnostically cleaner"

sample of controls (Cohen $d = 1.28 > 1.00$) than the total control group that included adolescents in which a parent had an episode of depression, illustrating the tradeoffs inherent in control group selection. In addition, although the ES for activation in the right parietal cortex (BA 7) was equally large ($d = 1.08$), the effect was not significant ($P = .20$). No other brain areas were significantly different between groups. This study therefore constituted an unambiguous replication of the increased right dorsal PFC (BA 46) activity reported by Callicott and colleagues in a sample of younger relatives still at risk for developing psychosis.

These findings were extended using another frequently used working memory task, the Sternberg item recognition paradigm[58] to examine 8 persons with schizophrenia, 10 nonpsychotic cotwins (4 monozygotic, 6 dizygotic), and 13 healthy control twins who were demographically similar.[54] In this task, a target set of 3, 5, 7, or 9 yellow letters was displayed for 2 s, followed by a 3-s period of fixation. A green letter then appeared for 3 s, followed by a 1-s period of fixation before the next trial. Subjects indicated whether the green letter matched any of the yellow letters in the target set. There were no group performance differences as a function of working memory load, but when data were collapsed across load, controls performed better than patients' nonpsychotic cotwins, who performed better than patients. While the authors reported no group differences in activity in anatomically defined dorsal PFC, parietal, and occipital cortices, they did find that the patients and their nonpsychotic cotwins exhibited different performance-activity correlations than controls; for patients and their twins, more activity was associated with worse performance, whereas the opposite was true of controls. In the contrast of patients' twins to controls, this difference in correlations reached significance in the left posterior parietal cortex, with dorsal PFC and right parietal cortex showing strong trends in this direction as well. While these findings do not constitute a direct replication of previous findings of hyperactivity, they are generally consistent with the theory that compensatory neural processes are associated with the genetic liability to schizophrenia. Moreover, with a modest sample of 10 unaffected twins, it is possible that meaningful findings are limited by inadequate statistical power.

Working Memory Summary. Of the 5 available studies to date, 4 contrasts showed increases in the right dorsal PFC region of interest, generally BA 46, in the relatives of schizophrenia patients, whereas 1 contrast was not significantly different and yet another contrast showed the opposite trend. Of the 8 regions of interest highlighted on table 2, the increase in right dorsal PFC showed the most consistent trend (67%), with increases in bilateral ventral PFC (67%) and decreases in bilateral cerebellum (60%) also prominent. If abnormality is defined as either an increase or decrease and irrespective of laterality, dorsal PFC, ventral PFC, parietal and lateral temporal cortices, and cerebellum all showed abnormalities in over 67% of reported contrasts. At a qualitative level, it appeared that the verbal tasks yielded the most consistent pattern of hyperactivity in right dorsal PFC, and the nonverbal or spatial tasks generally led to decreased activity. Interestingly, only one of the studies found significant performance impairments in relatives compared with controls,[54] though there were clearly trends in this direction in other studies, eg,[52] because all these studies involved block designs, they were rarely able to examine the component processes involved in executing a working memory task.

Long-Term Memory Studies

Episodic Memory. Episodic memory is the ability to learn and retrieve new information and has been dissociated both theoretically and empirically from other memory systems (eg, declarative, procedural, working memory) in terms of both behavior and neural substrates.[59,60] A large number of studies have suggested that individuals with schizophrenia demonstrate deficits in episodic memory,[61] including processes such as relational binding[62–65] and the use of elaborative encoding strategies that impair the use of recollection at retrieval.[65–69] A large body of research also suggests the presence of behavioral deficits in episodic memory among patients' relatives,[16,70,71] and there is some evidence that these deficits are stable over time.[45] The results of functional imaging studies of episodic memory in the nonpsychotic relatives of schizophrenia patients are summarized in table 3.

The first report of episodic memory impairments in patient's relatives, from researchers at the Edinburgh High-Risk Study, used an incidental encoding paradigm.[72] In this task, participants made abstract-concrete judgments about English words (so-called "deep" encoding) that was compared with old-new judgments ("shallow" encoding). The advantage of this kind of incidental learning paradigm is that it reduces any confound from self-generated strategies. There were no performance differences across groups in either task. Patients' relatives tended to show increased activity compared with controls in right, but not left, dorsal, and ventral PFC (BA 9/45), whereas they showed significantly greater activity in the cerebellum during retrieval. When this effect was examined for the relatives with and without "isolated" psychotic symptoms (ie, they had "subthreshold" or "prodromal" symptoms but did not meet criteria for any disorder), the controls only differed significantly in right BA 45 and only in contrast to relatives with occasional psychotic symptoms. The authors suggest that the enhanced right ventral PFC activation in relatives may represent *compensatory* right-sided activity to offset possible deficits in the typically left-sided activations

Table 3. Functional Neuroimaging Family Studies of Memory

First Author, Year	Primary Task	Design	No. of Relatives	No. of Controls	Relatives' Age	Perf.	Brain Activity								Other Brain Activity
							ACC	DPFC	VPFC	Parietal	Temporal	BG	Thalamus	Cerebellum	
Episodic memory															
Whyte et al (2006)[72]	Verbal encoding and retrieval	Event	68u	21	26.0*	=	Ø	↑*R* =L	↑*R* =L	=RL	Ø	=RL	=RL	↑R, =L	=RL 6
Bonner-Jackson et al (2007)[73]	Verbal encoding	Block	21s	38	21.1*	=	Ø	=L	↑RL	Ø	Ø	Ø	Ø	=R	=L 6 =RL 18
Thermenos et al (2007)[74]	Sentence generation	Block	21 s and o	26	19.9*	=	=R	=R	=RL	=R	=L	Ø	Ø	=	↑RL parahippocampus =RL hippocampus
Procedural memory															
Woodward et al (2007)[75]	Serial reaction time	Block	12s	15	36.9*	=	=RL	↓RL	=L	↓L	=R ↓L	↓RL	↓R	Ø	↓L parahippocampus, =LR 6 =L 18
Summary	↑ ↓ =						2R,1L	1R 1R,1L 1R,2L	2R,1L 1R,3L	1L 2R,1L	1L 1R,1L	1R,1L 1R,1L	1R 1R,1L	1R 2R,1L	

Note: Abbreviations are explained in the footnotes to table 1. Asterisk indicates where the mean age of relatives was not meaningfully different from controls ($P > .10$).

associated with semantic elaboration; however, there was no evidence of decreased left-sided activity in relatives. An alternative explanation is that increased right-sided inferior frontal activation in high-risk participants reflected decreased language-related lateralization, reviewed further below.

A subsequent study by Bonner-Jackson and colleagues[73] used a similar paradigm to examine episodic memory in the nonpsychotic siblings of individuals with schizophrenia. This study used a blocked design to compare deep encoding (abstract-concrete judgments like those used in the Whyte study) compared with shallow processing (first/last letter of the word alphabetical judgments). There were no group differences in performance on the abstract-concrete task judgments or subsequent recall; however, relatives had lower accuracy in alphabetical judgments and other neuropsychological indices of memory impairment. In addition, both controls and relatives showed a strong and similar "levels of processing" effect, which is enhanced recognition of words encoding in the deep vs shallow condition. Like Whyte and colleagues, Bonner-Jackson did not find any regions in which controls showed greater activation than relatives. Bonner-Jackson also found that the siblings again showed increased activation compared with controls during deep encoding in both right and left ventral PFC (BA 47). In support of the conjecture that this reflected compensatory activation in support of adequate behavioral performance, the authors demonstrated that the pattern of enhanced encoding-related activation was greater in higher than lower performing siblings. A drawback to the Bonner-Jackson and colleagues study was that it used a blocked design and thus could not separate out correct from incorrect trials during encoding, though the lack of overall group differences in task-related performance helps to mitigate this concern.

A recent study by Thermenos and colleagues[74] took a somewhat different approach to examining elaborative semantic processing effects in episodic memory in the first-degree relatives of individuals with schizophrenia using essentially the same sample of adolescents and young adults reported by Seidman and colleagues.[53] These researchers used a blocked paradigm in which participants were asked to silently generate sentences to pairs of either novel words or repeated words. This sentence generation paradigm focused on more relational or binding aspects of episodic memory, that may be mediated by hippocampal processing, in that the task required the integration of both words into a single sentence. Further, a comparison of novel word pairs and repeated words pairs allowed the authors to examine the integrity of repetition suppression and repetition enhancement effects that may contribute to episodic recognition. As before, there were no differences between the controls and relatives in recognition task performance in the scanner; however, relatives had reduced recall on the

Miller-Selfridge verbal memory task administered outside the scanner. Compared with controls, the relatives showed greater repetition suppression in bilateral anterior parahippocampus. This effect in part reflected the fact that controls actually showed *enhanced* activity with repetition in these regions. This group difference was eliminated when individual differences in Miller-Selfridge performance was entered as a covariate. In addition, when low-performing relatives were compared with high-performing relatives and controls, they showed less repetition suppression in left inferior frontal gyrus and left occipital gyrus. However, because the controls were not grouped into high and low performing, it is not clear whether these performance relationships were unique to at-risk populations or a more general effect. One drawback to this study was the use of a silent sentence generation task that did not allow for explicit assessment of encoding integrity. Thus, it is not clear to what extent the pattern of results reflects changes in the ability of relatives (either as a group or the low-performing ones) to generate effective sentences or to utilize the same or different sentences upon repeated stimulus presentation.

Procedural Memory Studies. In addition to the large literatures on working memory and episodic memory, there are a growing number of studies of procedural memory in schizophrenia. Procedural memory is the ability to acquire a motor or cognitive skill without explicit awareness. Studies of procedural memory in schizophrenia have been mixed, with some studies findings impairments[76] and other not,[77,78] though these differences may reflect the type of medications being taken by patients (as typical antipsychotics may impair procedural learning)[79–81] and stage of illness.[82] Functional imaging studies of procedural learning in schizophrenia have provided somewhat more consistent results, with evidence for reduced striatal activity in patients taking both typical and atypical antipsychotics.[76,78,83] Only one imaging study of procedural learning has been conducted in relatives of individuals with schizophrenia, and it is also included in table 3. Woodward[75] studied 12 siblings of individuals with schizophrenia and 15 controls using the same Serial Reaction Time task examined in individuals with schizophrenia.[78] In this task, participants learn a pattern of movements outside of awareness. Behaviorally, the siblings of individuals with schizophrenia showed clear evidence of implicit learning and did not differ from controls on behavioral performance of the task. However, in the imaging data, the siblings demonstrated reduced activity in several regions of dorsal PFC (BAs 9 and 10) as well as several basal ganglia regions in the comparison of sequenced to random strings of stimuli. Such results suggest that some vulnerability in the systems supporting procedural learning may be present in individuals at genetic risk for schizophrenia, even though such deficits are not severe enough to lead to clear behavioral abnormalities.

Long-term Memory Summary. There have been relatively few studies of episodic memory in high-risk participants, so it is premature to draw strong conclusions. Two contrasts show increases in relatives in the right ventral PFC, and 1 contrast was not significantly different. For left ventral PFC, 1 contrast showed increases in relatives, whereas 3 showed no differences. As noted above, this pattern may reflect a more general effect or reduced language-related lateralization in individuals with schizophrenia and those at risk for this illness. Given the role of hippocampus in episodic memory and findings of hippocampal volume reduction in both patients and relatives,[84] it was expected that the fMRI studies of episodic memory in relatives would reveal functional deficits in this region. However, none of the studies reported group differences in hippocampal activity (including a direct region of interest analysis[74]). Instead, there was preliminary evidence for increased parahippocampal gyrus activity in relatives, which may be suggestive of worse recognition performance. Although in-scanner performance was not different between controls and relatives, 2 studies found evidence for reduced recall on tasks outside of the scanner. Such results suggest that familiarity-based recognition mechanisms may be intact among high-risk individuals, but that explicit recollection mechanisms may be more impaired.

Language Processing Studies

Another domain of cognition in which individuals with schizophrenia have been shown to have deficits is language processing. There are a number of studies that suggest impairments in the ability to generate or initiate verbal productions. In the clinical domain, this is manifest as poverty of speech.[85] In the experimental domain, this has been assessed using a variety of paradigms, including categorical and phonological fluency and sentence completion.[86,87] Although we are describing this domain as language processing, such deficits in verbal production could clearly reflect a more general deficit in cognitive control or working memory.[88] However, there is also a body of research, suggesting some alterations among individuals with schizophrenia in processes that may be more ''language specific,'' such as reduced hemispheric laterality during a variety of lexical and phonological processing paradigms.[89–94] The results of functional imaging studies of language processing in the nonpsychotic relatives of schizophrenia patients are summarized in table 4.

The first study to examine language processing in individuals at risk for schizophrenia examined obligate carriers, who were individuals with both offspring and relatives in preceding or contemporaneous generations

Table 4. Functional Neuroimaging Family Studies of Language Processing

First Author, Year	Primary Task	Design	No. of Relatives	No. of Controls	Relatives' age	Perf.	Brain Activity								Other Brain Activity
							ACC	DPFC	VPFC	Parietal	Temporal	BG	Thalamus	Cerebellum	
Spence et al (2000)[95]	Phonological fluency	Block	10u	10	55.4*	?	Ø	=L	Ø	Ø	= L	Ø	Ø	Ø	↓ Correlation
Sommer et al (2004)[89]	Verb generation	Block	12t	12	42.0*	=	Ø	Ø	↑R =L	↑R =L	↑R =L	Ø	Ø	Ø	DPFC-occipital
Li et al (2007)[96]	Lexical decision	Block	15s	15	21.7*	?	Ø	Ø	↑R, =L	↑R =L	↑RL, ↓R[a]	Ø	Ø	Ø	
Whalley et al (2004)[97]	Hayling	Block	69u	21	26.1*	=	↓RL	↓R	=RL[b]	↓R↑L	↓R	Ø	↓RL	↓L	↓RL 31
Summary	↑								2R	2R,1L	2R,1L				
	↓						1R,1L	1R 1L		1R	2R		1R,1L	1L	
	=								1R,3L	2L	2L				

Note: Abbreviations are explained in the footnotes to table 1. Asterisk indicates where the mean age of relatives was not meaningfully different from controls ($P > .10$).
[a]↑RL in superior temporal gyrus (Brodmann area [BA] 22) and ↓R in middle temporal gyrus (BA 21).
[b]From figure 1a and 1b.

with schizophrenia, as well as individuals already ill with schizophrenia.[95] Brain activation during a phonological fluency task was compared with a control repetition task using PET. Spence and colleagues found that all 3 groups exhibited the expected activation in dorsal PFC and deactivation in superior temporal gyrus. There were no significant differences between obligate carriers and controls in activity, though they did find a reduction in the correlation between activity in left dorsal PFC and precuneus in the obligate carriers.

In subsequent work, Sommer and colleagues examined language lateralization in the discordant monozygotic twins of individuals with schizophrenia.[89] As noted above, a consistent body of work suggests that individuals with schizophrenia show reduced language-related lateralization, primarily reflecting increased right-sided activations in response to language demands.[89–94] Sommer and colleagues found the same pattern in patients' unaffected twins who were instructed to subvocalize a verb for each noun that appeared on the screen. In addition, they were to respond with a button press if the noun was an animal, which groups perform equally well. Unaffected twins showed reduced laterality indices across a range of brain regions associated with language function, including left inferior frontal cortex, superior temporal gyrus, and the supramarginal gyrus. Like their cotwins with schizophrenia, the high-risk individuals did not differ from controls in left-sided activation but showed increased right-sided activation.

Li and colleagues[96] also examined language-related activation in controls, probands with schizophrenia, and their siblings. This study compared activation during a lexical decision task that included both words and pseudowords to activation during a nonlinguistic control task. The controls, but not the patients or their siblings, showed greater activation in left inferior frontal cortex (BA 44) in the lexical decision compared with control tasks. The patients and siblings showed activation in BAs 44 and 45 for both tasks. In a comparison of the combination of the 2 tasks to rest, Li and colleagues found that compared with controls, both patients with schizophrenia and their siblings showed greater activation in right inferior frontal gyrus (BA 44), right inferior parietal lobe (BA 40), and superior temporal gyrus (BA 22). In addition, both patients and their siblings showed reduced activation in fusiform gyrus, though the laterality and extent differed across groups. These greater right-sided activations could reflect reduced language-related lateralization in individuals with schizophrenia and their high-risk siblings, similar to the results of Sommer and colleagues. However, given that lateralization was not explicitly examined in Li and colleagues, it is difficult to determine the exact patterns of activation giving rise to these results. In addition, no behavioral data was collected during scanning, making it difficult to determine whether or not these increases in activation might reflect

compensatory activity. However, the authors did report that all participants performed well outside the scanner.

The Edinburgh High-Risk study used a version of the Hayling Sentence Completion task to study verbal production in relatives.[97] In the Hayling, participants are presented with sentences missing their final word that vary in the degree to which this final word is constrained or predicted by the sentence context (low, medium low, medium high, high constraint). All the relatives had at least 2 first- or second-degree relatives with schizophrenia, and some were moderately symptomatic. Relatives did not differ from controls in reaction times to indicate when they covertly completed each sentence. In a parametric analyses that examined the effects of decreasing constraint (increasing difficulty), controls showed greater increases with difficulty than all relatives in right middle frontal gyrus (BA 10/32), left cerebellum, and bilateral thalamus. Further, compared with asymptomatic relatives alone, controls showed greater activity as a function of difficulty in right medial frontal gyrus (BA 10/32), bilateral posterior cingulate (BA 31), left cerebellum, right middle temporal gyrus, and right inferior parietal lobe. There were no regions that differed between symptomatic and asymptomatic as a function of difficulty relatives; however, when comparing all sentence completion conditions to rest, symptomatic relatives showed greater left parietal lobe activation than asymptomatic relatives or controls. A major strength of the study was the ability to examine differences that may be more or less associated with trait-like aspects of vulnerability vs more state-like aspects associated with the emergence of psychotic symptoms. A second strength of this study was the inclusion of individuals with at least 2 relatives with schizophrenia, potentially generating a sample more ''enriched'' in terms of genetic vulnerability to schizophrenia. However, there remain interpretive challenges. First, although the study required button presses on which groups performed equally, this did not actually measure the word generation, which was covert. It was somewhat comforting that word appropriateness scores were then derived outside the scanner. Second, the exact pattern of changes in brain activity in the relatives in the parametric contrast is unclear. The reduced estimates in high-risk participants reflect reduced increases in activation as a function of task difficulty. However, this pattern could occur in at least 2 different ways. First, it could be that controls and high-risk individuals do not differ in the high constraint condition (low difficulty), but high-risk participants fail to increase activation as a function of difficulty, leading them to show reduced activation at high difficulty levels. This pattern would be consistent with studies in patients with schizophrenia showing reduced activity during difficulty or high load conditions. In contrast, it could be that high-risk participants showed increased activation at low-difficulty levels and then do not further increase activation at high levels (potentially not differing from controls at higher levels). Such a pattern would be consistent with studies, suggesting enhanced activation in individuals with schizophrenia at low memory loads or low task difficulty (shifted response curve). These different patterns could have very different interpretative implications for understanding the nature of altered difficulty- related brain activation in individuals at risk for schizophrenia and thus clarifying the precise pattern of deficits is critical.

Language Processing Summary. The tasks and paradigms used to study language processing in relatives across studies have been very different, making it difficult to directly compare results. However, the edges of a pattern have begun to emerge: right ventral PFC and parietal and lateral temporal cortices were frequently abnormal in relatives. Increased activity was observed in relatives in right ventral PFC in 2 contrasts and equal activity in 1, whereas left PFC showed no differences in 3 contrasts. Similarly, in right parietal cortex, relatives showed increased activity in 2 contrasts and reduced activity in one other. In right temporal cortex, 2 contrasts showed increased and 2 showed decreased activity in relatives. These patterns could be seen as consistent with reduced language-related lateralization in high-risk participants, similar to results reported in patients with schizophrenia.[89,96] Like already ill individuals, this reduced lateralization seemed to reflect increased right-sided activations but fewer changes in left sided activations. It was not clear whether these increased activations indicate compensation, although the fact that most studies find no behavioral differences between high-risk participants and controls hints at such a possibility. Unfortunately, the studies tended to use paradigms that did not include a measurable behavioral response or did not report the results of the activation tasks, making it difficult to evaluate the influence of behavior on the results across studies.

Interpretation and Conclusions

State of the Literature

At 20 studies across 4 cognitive domains, the current database of neuroimaging studies of schizophrenia patients' nonpsychotic relatives is small by the standards of the literature in patients, but it is growing quickly. Most of the studies reviewed were either in press or published within the past 2 years. This literature is broadly consistent with findings using other methods, such as neuropsychology and cognitive psychology, electrophysiology, and structural imaging, in indicating that brain and cognitive functioning is altered in persons at genetic risk for schizophrenia. This suggests that a significant portion of the variance in abnormal brain functioning in schizophrenia patients is independent of the psychotic disorder per se.[9] These studies have evaluated functioning in

a number of regions but have rarely used the same task. Nonetheless, 80% of the studies reviewed were sensitive to dorsal PFC and parietal functioning, and 70% were sensitive to ventral PFC functioning. Activity was also observed across multiple studies in lateral temporal cortex (60% of studies), thalamus (60%), anterior cingulate (55%), cerebellum (50%), and basal ganglia (40%). As summarized in tables 1–4, evidence for altered functioning was found across all these regions. Occipital and precentral cortices were also commonly observed to be activated in these studies (45% of studies for each), but differences between groups in these regions were less common (about 33% of contrasts for each). Given the importance of understanding etiology of schizophrenia, how should we describe what we see through these windows into the brain functioning of individuals with unexpressed genetic liability?

To answer this question, we will consider the current evidence for group differences from 2 perspectives. One focuses on the consistency of the directionality of the findings across regions, whereas the second focuses more generally on the regions in which abnormalities are found. As for the consistency of findings, there were generally more increases in activation in relatives than decreases. Exceptions to this trend were found in the basal ganglia and cerebellum. In right ventral PFC, the region which most often showed increased activity in relatives, 8 (67%) contrasts showed this pattern, 4 contrasts (33%) showed no difference between relatives and controls, and none showed reduced activity (sign test $P = .008$). In right parietal cortex, the next most consistently altered region, 7 (54%) contrasts showed increased activity, 4 (31%) showed equal activation, and 2 (15%) showed decreased activity (sign test $P = .18$). In the frequently observed right dorsal PFC, 8 (50%) contrasts showed increased activity in relatives, 3 (19%) showed no differences, and 5 (31%) showed decreases. The other regions trailed further behind when taking into account hemisphere and directional consistency. From this perspective, 14 of the 16 regions we tracked by hemisphere did not appear to have a consistent, directional relationship with the genetic liability to schizophrenia. To the extent that there was a reliable signal associated at all, it was most evident as an increase in brain activity in a very few regions of the right hemisphere, a finding that is relatively uncommon in the schizophrenia literature itself. Indeed, though patients are often found to have reduced activity, rather than increased activity, in such PFC regions, and there is little evidence that this is expressed more in the right hemisphere than in the left, except for in studies of language function.[48,98,99]

The second perspective is more inclusive. If "abnormality" is defined as *any* difference between relatives and controls irrespective of the direction of that difference, the study of relatives has unveiled several regions in which functional abnormalities may be associated with genetic liability to schizophrenia. Five regions, collapsed across hemisphere, show such abnormalities in about two-thirds of within-region contrasts: cerebellum (13 of 18 contrasts, 72%), dorsal PFC (20 of 28 contrasts, 71%), lateral temporal (14 of 21 contrasts, 67%) and parietal cortices (19 of 29 contrasts, 66%), and thalamus (13 of 20 contrasts, 65%). These regions have also been found to have abnormally (generally reduced) activity in schizophrenia patients with moderate ESs.[48,98] A second tier of regions showed group differences in about half of studies: basal ganglia (7 of 13 contrasts, 54%) and ventral PFC (13 of 26 contrasts, 50%). The anterior cingulate, on the other hand, showed altered activity in only 8 of 21 (38%) contrasts. Although these contrasts are not all independent (in some cases derived from the same analyses), they are consistent with the idea that the unexpressed genetic liability to schizophrenia involves a widespread disruption in regional activity or in cortico-cortico, cortico-thalamic, and cortico-cerebellar connectivity. In contrast to results addressed from the perspective of consistency of findings, the prominent ventral PFC alterations from this more inclusive perspective appears reduced because activity in the *left* (rather than right) ventral PFC does not generally differ across groups (equal activation in 9 of 15 studies, 60%). However, it is important to note that the percentages reported above are based on just a few studies, with the method of analysis and data reporting varying greatly across studies. It is possible that had results been reported differently or statistical thresholds been determined in different manner in even a few studies, the rank ordering of regions in terms of consistency of impairment might shift considerably.

Given these 2 perspectives, which interpretation of findings to date is more valid? Proponents of the directionally consistent perspective can argue that ignoring direction of group differences is scientifically repugnant. First, it assumes that the impact of liability genes must be observed in brain activity, such that any group difference is interpretable as a real finding, rather than noise. Funnel plots or other meta-analytic tools that count only the absolute value of a finding would be biased toward finding differences where no true differences exist. Further, one may well contend that directionality is an important source of hypotheses: hyperactivity may indicate inefficiency or a cognitive reserve that is protective for relatives, while hypoactivity may indicate altered strategies or specific types of impairments that preclude adequate function of a region. These different hypotheses may reflect very different pathophysiological mechanisms and thus may have important implications for our future understanding the nature of the underlying system and genetic expression.

While an emphasis on consistency in direction would seem to be the principled high ground, it also misses several key considerations about the nature of the complex

analyses being performed. General linear models are fully capable of leading to different observations in the same populations. For example, Dellawalla and colleagues[31] reported increased dorsal PFC as main effect of group, where decreased dorsal PFC was observed in interaction with delay. Is this hyper- or hypoactivity? That depends on whether you are interested in the main effect of group or its interaction with delay, which researchers outside this subfield are unlikely to find an especially generative question. The same observation can occur when considering the effect of covariates. Thermenos and colleagues[29] report that including covariates reversed the direction of effects in dorsal PFC and hippocampus, turning hyperactivity to hypoactivity. How should this be understood? Hemisphericity and regional heterogeneity are also common occurrences in this literature, such that increases are observed in one hemisphere or in one area, whereas a similar region on the opposite hemisphere or a near-by region in the same hemisphere shows the opposite pattern. Finally, increases or decreases can occur across different tasks and contrasts within the same sample.[100,101] For example, MacDonald and colleagues[32] found decreased activity in right dorsal PFC when preparing to overcome a prepotent manual response, whereas Becker and colleagues[28] found increases in this region in the same participants when overcoming a prepotent Stroop response. A proponent of the inclusive perspective would argue that the direction of altered activity may interact in important ways with memory load or other task demands and that strict attention to the direction of abnormality is premature and could preclude an understanding of the central gist of this literature.

How might this impasse be resolved? Well, one might simply conclude that, after a decade of investment into this research, the lack of a definitive signal at this point is evidence that liability genes do not have any consistent impact on brain functioning. This interpretation suggests that the endeavor of imaging genetic liability is of limited utility. However, it is hard for us to conceive that the consistent patterns of performance deficits known to exist in this population[9,16] would occur were there not impairments in brain functioning. Despite relative homogeneity of samples, there are many heterogeneous subject characteristics that could be influencing outcome. We address this issue in the context of issues specific to functional imaging studies per se. A more promising way to move forward may be to conclude that the nature of genetic expression is complicated by the capacity to overcome deficits when sufficiently motivated and that the methods used in this field to date are as yet insufficient to capture this subtlety. As a field, we have not yet overcome the challenges of experimental design, analysis, and reporting that will allow us to detect the signature of genetic liability consistently across studies. This suggests a need to change the way in which studies of unexpressed genetic liability are analyzed and presented in future work.

Implications for Methodological, Analytical, and Reporting Practices

The inherent complexity of functional neuroimaging increases the risk that such studies will fail to mesh into a cumulative science. Differences in tasks, in different cognitive demands within a trial, in event-related vs block-designed task presentation, in device field strength, analytical software, and even data preprocessing decrease the likelihood of replicating findings across laboratories. Indeed, investigators themselves have rarely attempted to replicate their findings with an identical methodology. Thus, despite many uncontrolled sources of variance, we believe much can be done to strengthen the literature in this field. We offer the following methodological refinements for consideration not from a position of advantage or abstraction. Instead, the recommendations summarized on table 5 are a response to concerns that have evolved organically while struggling separately and together to make sense of our own data and that of others. To this end, 3 methodological and analytic adjustments suggest themselves:

1. Apply symmetrical inclusion/exclusion criteria across relatives and controls (other than family history of psychosis): Ideally, any differences between relatives and controls can be unambiguously attributed to the unexpressed genetic liability to schizophrenia. However, a number of studies have used asymmetrical exclusion criteria and recruitment procedures, such that the other systematic differences between the control group and the relatives of individuals with schizophrenia may drive observed differences. Such differences may include factors such as nonschizophrenia-spectrum axis I or axis II diagnoses that are allowed to be present in relatives, but not in controls, ''volunteerism,'' or other characteristics that may distinguish groups.[102] In a meta-analysis of behavioral data, the use of asymmetrical inclusion criteria magnified the measured ESs by a statistically significant 30%.[16] Seidman and colleagues[53] demonstrated the impact on ES of making the groups asymmetrical by secondarily excluding controls with a family history of depression. This manipulation had a modest impact on ES (0.28), but this could be large enough to change a finding's significance. As such, it is possible that some of the variability in results across studies reflect variability in the inclusion/exclusion criteria utilized.
2. Use tasks that allow behavioral responses to be recorded during scanning: Some of the variability in results across studies may also reflect differences in the difficulty of the tasks utilized or the performance levels of the relatives as compared with the controls. While there continues to be a debate in the field about the benefits and risks of matching performance for a scanned task, most agree that measuring performance improves the interpretability of imaging results.

Table 5. Summary of Design, Analysis, and Reporting Recommendations for Imaging Studies of Nonpsychotic Relatives

Design and analysis recommendations	
1	Apply symmetrical inclusion/exclusion criteria across relatives and controls (other than family history of psychosis)
2	Use tasks that allow behavioral responses to be recorded during scanning
3	Evaluate regions of interest as well as voxelwise exploratory analyses
Reporting recommendations	
1	Explicitly present relevant statistical criteria, such as voxel or region-wide thresholds, cluster size, etc.
2	Report regions activated in the entire sample (or at least the control group alone) to identify the network activated by the task
3	Report ESs for behavioral and imaging data
4	Quantify the risk of false-negative results
Future enhancements	
1	Explore the heterogeneity among relatives
2	Evaluate the relatives of psychiatric control groups
3	Validate brain activity as an endophenotype, including estimating stability, heritability, and cosegregation

Either way, the next generation of neurogenetic studies will likely benefit from collecting and reporting behavioral data during scan acquisition.

3. Evaluate regions of interest as well as voxel-wise exploratory analyses: Adjustments in the manner in which analyses are conducted may also help to reduce variability across studies. Currently, most researchers start by conducting voxel-by-voxel analyses to discover group differences. While this is a perfectly reasonable approach, it does mean that comparisons across studies are limited to regions that show significance in each study at what are often fairly stringent "whole-brain correction" levels. This provides no information about regions that might show similar effects across studies, with the significance level just slightly below threshold in one or more of the studies. One approach that may be fruitful in future work is to conduct region of interest–based as well as voxel-based analyses. A region of interest–based approach is often more powerful and would provide a clearer understanding of similarities and differences across studies in the same regions of interest. This approach highlights the potential confound of brain structure differences spuriously suggesting activation differences. While a multimodal imaging approach that thoroughly examines the relationship between brain structure and functional activations has yet to be implemented, the evidence that does exist suggests that morphological differences between groups do not account for group differences in activity statistics.[103] Reporting the relevant means and standard deviations for data from such regions of interest (as well as any other regions of interest identified) will also provide information about ESs, regardless of whether the effect was significant. In addition, one might also explore whether these are regions with baseline differences in the BOLD response, eg, by obtaining perfusion images or examining default network activity.

As helpful as the above strategies may be, perhaps, the most important developments we can urge are changes in reporting practices that can help establish a cumulative science of neurogenetics of schizophrenia. Table 5 summarizes 4 approaches related to reporting practices that have the potential to increase our ability to compare results across studies and facilitate meta-analytic research:

4. Explicitly present relevant statistics: This seems obvious, but the details necessary to reconstruct an analysis strategy or compare analysis strategies across studies are too often missing from reports. The values used to threshold statistical maps should be reported, with a description of whether or not the threshold was corrected for multiple comparisons. Other statistics, including t, F, or Z values and P values should be reported, with clear description of how the P values were corrected for multiple comparisons.
5. Report the whole active network: In order to provide a context of regions activated by the task before between-group differences are interpreted, significant activations elicited by the target task should be reported for the control sample only, the relative sample only, or for the combined sample of controls and relatives (supergroup). While this practice can contextualize where group differences had the potential to be detected, one can bear in mind that this is generally a repeated-measures contrast. In most studies, this means there will be better power to detect the network activated by a task than to detect any group differences within that network (see approach #7, below). There is also growing recognition of the importance of deactivations associated with task performance. Reporting the deactivated network and group differences in this network may also provide valuable insights into the signature of the unexpressed genetic liability to schizophrenia.
6. Include ESs: Whereas thresholds and P values provide important information about the manner in which type 1 error rates were controlled, ES metrics provide additional information about the size of the differences that are detected regardless of sample size. For

example, 2 regions may both show significant differences between groups but have greater or smaller differences between groups. This is a useful addition to the increasingly common practice of reporting Z values or their equivalent as it facilitates a comparison across studies. ESs are also very useful for evaluating behavioral similarities and differences across groups.

7. Quantify the risk of false-negative results: When reflecting on the variability in results across studies, it is useful to bear in mind the risk of false-negative findings. Studies of patients' nonpsychotic relatives are likely to show smaller effects on brain functioning than similar studies in schizophrenia patients. Meta-analyses of behavioral studies suggest that patients perform on average about 0.92 standard deviations worse than controls across many cognitive tasks,[104] while the average ES in healthy relatives on the same metric with appropriate control groups was approximately 0.35.[16] By way of illustration, a patient study with these effects would require a sample size of 16 per group, whereas a study of relatives would require a sample size of 102 per group for power of .80 at alpha = .05. *In this case, a 2.5-fold reduction in the predicted ES resulted in a 6-fold increase in the required sample size.* The impact of the smaller effects in relatives suggests that proportionally larger samples will be required to obtain the same power as patient studies to detect group differences. Quantifying the ESs that must be present to detect differences in brain activity after making brain-wise or small-volume statistical corrections can help contextualize a negative finding and provide useful information for planning subsequent studies.

Many of these concerns are in no way unique to this domain of inquiry. Concern about reporting standards and the comparability of findings across studies have grown in recent years, leading to a movement for increased rigor in reporting standards.[105] However, in the process of preparing any such publication, a wealth of location-related and time frequency–related data is lost, as is most information about subthreshold activity. Raw data archives and support for neuroinformatics are likely to be needed to systematically recover these valuable data.[106]

While these kinds of clarifications can improve our capacity to discern patterns of function and dysfunction associated with the genetic liability to schizophrenia, future studies can make important new contributions by evaluating several additional aspects of the data. In particular, the following 3 directions could provide useful insights:

8. Explore the heterogeneity among relatives: In most studies included in this review, relatives have been treated as a homogeneous group. This is an assumption of convenience known to be false. One aspect of this heterogeneity is age. Relatives who have passed through the age of peak risk for schizophrenia (>age 30) allow the evaluation of components of the syndrome that are independent of psychosis. The study of younger relatives (<age 30) provides an opportunity to identify the neurobiological differences present prior to typical onset of schizophrenia in a subset of relatives. Younger relatives are likely to comprise a mixture of future cases and noncases, and therefore, the ESs here may be larger than in older samples where further onset of illness is unlikely. Studies of young family members can even contribute to prediction of illness.[107] A second source of heterogeneity among relatives is genetic load. Just as schizophrenia patients themselves vary as to the extent of their genetic load, so too do relatives. One way to do this is to examine the presence or absence of specific genetic markers. In this case, relatives with 2 copies or a single copy of a risk allele can demonstrate the impact of that allele within a "higher risk" genetic background. This may allow gene-by-gene interactions or other epigenetic effects associated with the risk allele to be highlighted, which may be overlooked in a study of the marker in the general population. Even in the absence of a specific genetic marker, genetic load can be measured in several ways. The most common manner of doing this is to estimate the number of schizophrenia patients in the relative's family; however, the age of onset of the patient probands has also been suggested as a proxy for genetic loading. Genetic "load" in relatives has been shown previously to affect symptoms and interpersonal behavior,[108] cognition,[109] and hippocampal volume.[84]
9. The third source of heterogeneity is the relatives' relationship to the proband. Offspring, siblings, and parents all carry essentially equal genetic risks (although parents may be more biologically "fit" because they have produced offspring) but different biological environmental risks (offspring and twins are more likely to suffer perinatal complications) and psychosocial risks (ie, growing up with ill parent vs recent onset of a siblings illness); obligate carriers, ie, parents through whom schizophrenia genes are assumed to be transmitted, and monozygotic twins are again special cases. The fourth and fifth sources of heterogeneity are derived from symptom presentations. The type of schizophrenia in the proband—how severe the case is or whether subjects are sampled from the community, chronic care hospitals, etc.[84,109] Similarly, the symptoms in relatives provide suggestive data about genetic liability. Even though they are not considered to be affected as a group, some studies have found as many as 50% of relatives have diagnosable nonpsychotic disorders. Thus, greater attention to subgroups (schizotypal vs nonschizotypal relatives, etc.) would also be beneficial.

10. Evaluate the relatives of psychiatric control groups. Studies that focus exclusively on one psychiatric disorder risk confounding disorder-specific vulnerabilities with the general vulnerability to mental illness. Thus, the logic of psychiatric control groups in patient studies applies just as well to family studies. There is also a unique strength that comes with using the relatives of other psychiatric disorders as a control group. This is the similarity of recruitment procedures. The evaluation of other psychiatric patients' relatives addresses a broad swathe of factors which may distort ESs in other studies, such as volunteer bias and the need felt among some relatives to emphasize the contrast between themselves and their psychiatrically ill relative.
11. Validate brain activity as an endophenotype, including estimating stability, heritability, and cosegregation. According to guidelines for establishing endophenotypes,[3] brain activity measures are only in the preliminary stages of validation. That is, there are measurable impairments in patients and in relatives. There is evidence from studies reviewed elsewhere[99] that many of these impairments have also been observed in first-episode patients (which minimizes medication and chronicity effects). However, none of the studies reviewed included estimates of stability over time or the heritability of these abnormalities. Only 2 tasks have been used in a replication study.[29,30,56] Thus, refining imaging phenotypes by replication, test-retest, and heritability studies remain important priorities. This work can also provide insight by allowing the heritability estimates of behavioral tasks to be compared with that of the underlying brain functioning. Studies that test both control probands and control relatives are well positioned to address heritability. The important relationship between heritability and power to detect genetic association has been described elsewhere.[110] Short of scanning an entire pedigree, the cosegregation of impairments can begin to be addressed in studies that scan patient probands and more than one relative. Even studies in which only the patient probands and a single relative are available contribute to understanding the nature of this endophenotype by evaluating whether the patients with the most abnormal brain functioning are also those with the most abnormally functioning relatives. A better understanding of the heritability of these endophenotypes and their cosegregation within families would go a great distance toward understanding how the unexpressed genetic liability to schizophrenia is manifest in the functioning brain.

The era of the human genome is bringing to bear many new ways of studying the genetic causes of schizophrenia. For example, a new hybrid analysis of functional imaging data has just been published which included schizophrenia patients, relatives, and controls and single-nucleotide polymorphisms (SNPs) from 15 different genes associated with the genetic liability to schizophrenia.[111] In this analysis, both familial relationship to the proband and risk allele status were taken into account to identify differential function associated with allelic status. Multiples genes have been evaluated in other studies (eg, Tan et al[112]), and the methodological challenges of such studies are increasingly well understood.[113] Fifteen genes may soon be seen as a relatively conservative number of genes to examine in an imaging genomics study. Even so, the signal in such analyses is likely to remain small relative to the number of comparisons conducted. Because no single study will be definitive, replication and the higher reporting standards required for meta- and mega-analyses are likely to become even more important in the coming decades.

Conclusions

Family study methods remain our most powerful tool for understanding the impact on brain and behavior of the unexpressed genetic liability to schizophrenia. The odds ratio of being diagnosed with schizophrenia of our most potent susceptibility genes to date hovers just fractions above 1. The odds ratio of a first-degree relative being diagnosed with schizophrenia compared with someone from the general population is about 10. Thus, while there is general excitement about the prospect of molecular neurogenetic studies,[110] ie, linking genetic polymorphisms to variation in brain function, such studies will suffer even more stringent power limitations. The difference in odds ratios between susceptibility genes and the quantitative genetic liability to schizophrenia in family members illustrates the importance of coming to grips with the family study literature: this literature can serve as a road map for understanding the impact of any SNP or haplotype, and the difficulties encountered in the studies reviewed here will resonate loudly in the domain of molecular neurogenetics studies.

From a direction- and hemisphere-specific perspective, increased activity in the right ventral PFC appeared as the most consistent signal, with increased activity in right parietal cortex also observed with some regularity. Other regions were less likely to show consistent patterns of increases or decreases within a given hemisphere. From a more inclusive perspective, which counted either increases or decreases from either hemisphere as abnormalities, the most consistently impaired regions were cerebellum, dorsal prefrontal, lateral temporal and parietal cortices, and thalamus. These regions showed abnormalities in about two-thirds of the nonindependent contrasts sensitive to group differences. This suggests a very broad impact of liability genes, consistent with findings in the illness itself. Of the regions we chose to track, only the

anterior cingulate cortex performed normally in the majority of contrasts. Abnormalities in the anterior cingulate often reported in schizophrenia may then be illness-state markers rather than the result of genetic liability.

A better understanding of the impact of the genetic liability to schizophrenia on brain functioning has important implications for the causes of schizophrenia. It provides a framework for thinking about how liability to the disorder is manifest, which neurotransmitter systems might be involved, and what cognitive mechanisms might be most fruitful to explore. This review struggled with the heterogeneity within this literature to determine whether a definitive story was emerging. The most definitive result of this effort has been the identification of a number of methodological, analytic, and reporting standards that can benefit the coming generation of studies of the patients' nonpsychotic relatives. This work is on the cutting-edge of understanding schizophrenia, and a more consistent approach to our data can better help build a more cumulative, coherent perspective on the pathophysiology of the genetic liability to schizophrenia.

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