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Neural correlates of verbal and nonverbal working memory deficits in individuals with schizophrenia and their high-risk siblings

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Abstract

Impaired working memory and functional brain activation deficits within prefrontal cortex (PFC) may be associated with vulnerability to schizophrenia. This study compared working memory and PFC activation in individuals with schizophrenia, their unaffected siblings and healthy comparison participants. We administered a "2back" version of the "nback" task. Functional MRI (fMRI) was used to measure brain activity. Nineteen individuals with DSM-IV schizophrenia, 18 of their siblings, and 72 healthy comparison participants underwent fMRI scans while performing word and face "nback" working memory tasks. Repeated trials (items whose prior presentation was not in the correct nback position) allowed us to assess group differences in the ability to code the temporal order of items. Individuals with schizophrenia and their siblings performed worse than controls on repeated lure trials, suggesting an association between schizophrenia and impairments in the coding of temporal order within working memory. Both individuals with schizophrenia and their siblings also demonstrated abnormal brain activation in PFC, such that both groups had hyperactivation in response to word stimuli and hypoactivation in response to face stimuli. These results provide further evidence that individuals with schizophrenia and their siblings are impaired in their ability to encode the temporal order of items within working memory and that disturbances in working memory and PFC activation may be genetic markers of the vulnerability to schizophrenia.

Keywords: Schizophrenia; Working memory; fMRI; High-risk; nback; Prefrontal cortex

1. Introduction

Individuals with schizophrenia have impaired working memory (WM) and functional brain activation deficits in dorsal–lateral prefrontal cortex (DLPFC) (Barch et al., 2001; Carter et al., 1998). Siblings of individuals with schizophrenia also demonstrate impaired WM (Glahn et al., 2003; Goldberg et al., 2003; Niendam et al., 2003) and similar abnormalities in the activation of WM-related cortical regions, including DLPFC (Callicott et al., 2003a). Such findings suggest that WM impairments are associated with genetic susceptibility for schizophrenia. However, only a few studies (Callicott et al., 2003a; Thermenos et al., 2004) have assessed deficits in cortical activation in siblings of individuals with schizophrenia, and the majority of these have studied siblings that had already passed the age period of risk for developing the disorder. Siblings who have passed the period of risk still exhibit cognitive deficits. However, since these siblings have not developed schizophrenia

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(and are unlikely to do so), they may have less severe cognitive impairments. Studying high-risk siblings *before* they have passed the age period of risk for developing the disorder increases the likelihood that the sample may contain some individuals who will go on to develop schizophrenia and thus may allow a more sensitive assessment of cognitive or functional brain abnormalities associated with risk for schizophrenia. Further, it is not clear whether abnormalities in WM performance and brain function among individuals who may be genetically susceptible to schizophrenia vary across word and face domains and in what way associated cortical dysfunction extends to regions other than PFC. Thus, the present study examined WM and brain activation in young siblings of individuals with schizophrenia (ages 14 to 25 years) using both word and face WM paradigms.

WM can be defined as the ability to temporarily maintain and manipulate information "on-line" (Baddeley and DellaSala, 1996). This set of cognitive processes is impaired in individuals with schizophrenia (Gooding and Tallent, 2001; Park and Holzman, 1992), particularly during tasks that require the manipulation of items (Barch et al., 2000; Callicott et al., 2003b; Jansma et al., 2004; Kim et al., 2004; Perlstein et al., 2003) and/or the temporal coding or sequencing of items (Barch et al., 2000; Callicott et al., 2003b; Gold et al., 1997; Jansma et al., 2004; Meyer-Lindenberg et al., 2001; Perlstein et al., 2001, 2003). A consistent finding in functional imaging studies is that DLPFC activity is altered during WM tasks in individuals with schizophrenia as compared to healthy controls and other clinical populations (Barch et al., 2003). The DLPFC is thought to be particularly important for the manipulation and temporal coding of information in WM (D'Esposito et al., 1999; Owen, 1997; Owen et al., 1998; Petrides, 1996). However, some studies suggest DLPFC hypoactivation (Andreasen et al., 1992; Barch et al., 2001; Callicott et al., 1998; Weinberger and Berman, 1996) possibly due to limited capacity constraints (Jansma et al., 2004). In contrast, other studies suggest DLPFC hyperactivation (Callicott et al., 2000; Manoach et al., 1999, 2000; Ramsey et al., 2002) that may reflect compensation for functional impairments in the WM system (Callicott et al., 2000).

Many studies also suggest functional activation impairments in other WM-related brain regions among individuals with schizophrenia, including parietal cortex, thalamus and cerebellum (Kubat-Silman et al., 2002; Schlosser et al., 2003). For example, abnormalities in a cortico–cerebellar–thalamic–cortical circuit (Andreasen et al., 1999) have been proposed as an explanation for cognitive dysfunction or "dysmetria" in schizophrenia. The thalamus plays an important role in tasks where sequencing demands are high, and the cerebellum seems to be involved with the sequencing of words and phrases at a speaker's habitual speech rate (Ackermann et al., 2004). Given these normative functions of the thalamus and cerebellum, disturbances in this circuit among individuals with schizophrenia might contribute to disturbances in the ability to encode the temporal order of items in WM tasks in which the sequencing demands are high. Additionally, the dorsal inferior parietal cortex has been hypothesized to play a role in the maintenance of temporal order in working memory (Marshuetz et al., 2000) and is sensitive to load effects during manipulation of an nback task (Ravizza et al., 2004).

A number of studies have also shown that first-degree relatives of individuals with schizophrenia, who have increased genetic susceptibility to schizophrenia, exhibit impairments in WM performance (Cannon et al., 2000; Conklin et al., 2000; Goldberg et al., 2003; Park et al., 1995). A few studies have also reported abnormalities of brain activation in first-degree relatives during WM tasks. However, these results have been mixed, with Keshaven and colleagues reporting *decreased* DLPFC and parietal activation during a spatial WM task (Keshavan et al., 2002) in the offspring of individuals with schizophrenia, and others reporting *increased* activation during verbal WM in DLPFC, anterior cingulate, thalamus (Callicott et al., 2003a; Thermenos et al., 2004) and cerebellum (Callicott et al., 2003a) in siblings and parents that are already past the risk period for developing schizophrenia. Thus, it is not clear whether the differences across these studies are due to task type (spatial WM may elicit more severe DLPFC deficits) or differences in the samples (children in the Keshavan study, adults in the Callicott and Thermenos studies, many of whom may have been past the period of risk).

The goal of the current study was to examine functional brain activation during a word and face WM paradigm in siblings of individuals with schizophrenia that were still within the age of risk for developing the disorder. We administered word and face versions of the 2back WM task to individuals with schizophrenia, their siblings below the age of 26, and controls.

2. Methods

2.1. Participants

Participants were recruited through the clinical core of the Conte Center for the Neuroscience of Mental

Disorders (CCNMD) at Washington University in St. Louis, and included: 1) 19 individuals with DSM-IV schizophrenia (SCZ: 17 male, 2 female); 2) 18 siblings of individuals with schizophrenia (SIB: 7 males, 11 female); and 3) 72 healthy control participants (CON: 34 male, 38 female). The CON group was actually comprised of 36 sibling pairs. Similarities and/or differences between controls and their siblings were not the focus of this paper, and the results were essentially the same if the controls and their siblings were treated as separate groups. Further, all results reported below remained significant if the SIBs were compared just to control siblings as well as to the full sample of controls. Thus, we combined the controls and their siblings into a single group of controls to simplify the description and presentation of the analyses and results.

The SCZ participants were recruited from a variety of sources, including local inpatient and outpatient treatment facilities. CON participants were recruited using local advertisements in the same community. Exclusion criteria for CON included the presence of any lifetime history of Axis I psychiatric disorder or any first-degree relative with a psychotic disorder. The CON siblings and SIBs were recruited using the same exclusion criteria. They were excluded for any lifetime history of Axis I psychotic disorders (including Bipolar), but not other Axis I disorders. Potential participants were also excluded for: (a) meeting *DSM-IV* criteria for substance abuse or dependence within the past 6 months; (b) presence of any clinically unstable or severe medical disorder, or a medical disorder that would confound the assessment of psychiatric diagnosis or render research participation dangerous; (c) head injury (past or present) with documented neurological sequelae or resulting in loss of consciousness; and (d) meeting *DSM-IV* criteria for mental retardation (mild or greater in severity). Demographic information is displayed in Table 1. The SCZ group had significantly more males than the other groups, $X^2(2)=16.1$, $p=.001$]. The groups did not differ significantly on age [$F(2, 96)=.98$, $p=.38$], years of parent education [$F(2, 92)=2.45$, $p=.09$], or handedness [$F(2, 95)=1.217$, $p=.30$]. As shown in Table 1, WAIS-III Vocabulary scores were significantly lower in SCZ than CON ($t=3.34$). The vocabulary scores of SIBs fell in between those of SCZ and CON, but did not differ significantly from either SCZ ($p=.11$) or CON ($p=.96$). Diagnoses for all participants were determined using the Structured Clinical Interview for *DSM-IV* (SCID-IV; Spitzer et al., 1990), and were assessed using the Scales for the Assessment of Negative and Positive Symptoms (SANS/SAPS (Andreasen, 1983a,b). The clinical assessments were conducted by a master's-level research assistant who had completed SCID-IV training and participated in regular diagnostic and clinical rating training sessions as part of the CCNMD. The SCID-IV interviewer had access to all data from present and past hospital records and family sources. In addition, an expert clinician conducted a semi-structured interview, also using *DSM-IV* criteria and all available records. A consensus meeting between the SCID-IV interviewer and the expert clinician determined the participant's final diagnosis. The schizophrenia participants had been treated with antipsychotic drugs and their symptoms were stable for a minimum of 2 weeks. Handedness was assessed using the Edinburgh Handedness Inventory (Oldfield, 1971).

2.2. Tasks and materials

Participants performed a "2back" version of the "nback" task while being scanned, as well as episodic

Table 1
Demographic and clinical data

Characteristic	Controls		Schizophrenia		Schizophrenia siblings		Significance	
	M	S.D.	*M*	S.D.	*M*	S.D.	F/X^2	Sig
Age (in years)	20.3	3.5	21.6	2.9	20.7	4.0	.98	.378
Gender (% male)	47		88		39		16.1	.001
Parent's education (years)	15.5	2.3	14.9	2.7	14.1	2.2	2.45	.092
Participant's education (years)	13.1	2.7	11.7	2.2	12.2	3.0	2.20	.116
Handedness (% right)	84.6		82.4		88.2			
Mean SAPS Global Item Score	.03	.10	1.55	.59	.09	.19		
Mean SANS Global Item Score	.17	.30	2.00	.81	.43	.64		
Mean Vocabulary Scores	12.5	2.8	9.8	4.0	10.8	3.0	6.67	.002
Poverty Symptoms	.03	.08	2.07	.11	.29	.11		
Disorganization	.13	.08	2.69	.12	.52	.11		
Reality Distortion	.03	.09	2.40	.14	.11	.13		

encoding and retrieval tasks in the same session, the data from which are the focus of a different report (Bonner-Jackson et al., 2005). During the WM task, stimuli (words or faces) appeared one at a time on the screen and participants were told to push one button (target) any time they saw a stimulus that was the same as the stimulus they saw two trials back. If the stimulus was not the same as the one presented two trials back, they were told to push another button (non-target). Stimuli for the word tasks were concrete visually presented words, 3–10 letters in length, presented in 48 point Geneva font (see Fig. 1). Stimuli for the face tasks were non-famous faces (Barch et al., 2002; Braver et al., 2001; Kelley et al., 1998; Logan et al., 2002).

Participants performed each WM task in a run lasting 4.25 min. Each run included 4 task blocks of 16 trials each and 3 fixation blocks of 10 trials each interleaved in alternating order with the task blocks. In addition, there were 4 fixation trials at the beginning of each run that were discarded in the analysis of the data (used to allow MR signal to reach steady state) and 4 additional fixations at the end. Task blocks lasted 40 s and fixation blocks lasted 25 s. Each of the items in a task block was presented for 2 s followed by a 500 ms interstimulus interval. During fixation blocks, a cross hair appeared continuously and participants were told to fixate. Visual stimuli were generated by an Apple PowerMac and PsyScope (Cohen et al., 1993) and projected to participants with a Sharp LCD projector onto a screen positioned at the head end of the bore. Participants viewed the screen through a mirror attached to the top of the MR head coil. A fiber-optic key press interfaced with the PsyScope Button box was used to record participant's behavioral performance. The order in which participants performed the word versus face version of the nback task was counterbalanced.

2.3. Procedure

2.3.1. Scanning

Scanning was performed on the 1.5T Siemens VISION system at the Research Imaging Center of the Mallinckrodt Institute of Radiology at the Washington University Medical School. Functional images were collected using an asymmetric spin-echo echo-planar sequence sensitive to blood oxygenation level-dependent (BOLD) contrast (T2*) (TR=2500 ms, TE=50 ms, FOV=24 cm, flip=90°). During each functional run, 102 sets of oblique axial images were acquired parallel to the anterior–posterior commissure plane (3.75×3.75 mm in plane resolution). Nineteen 7 mm thick slices were acquired in each image. Structural images were acquired using a coronal MP-RAGE 3D T1-weighted sequence (TR=9.7 ms, TE=4 ms, flip=10°; voxel size=1×1×1.2 mm). These structural images were used for between subject registration and anatomic localization.

Preprocessing of the fMRI data included: (1) compensation for slice-dependent time shifts; (2) elimination of odd/even slice intensity differences due to interpolated acquisition; (3) realignment of data acquired in each subject within and across runs to

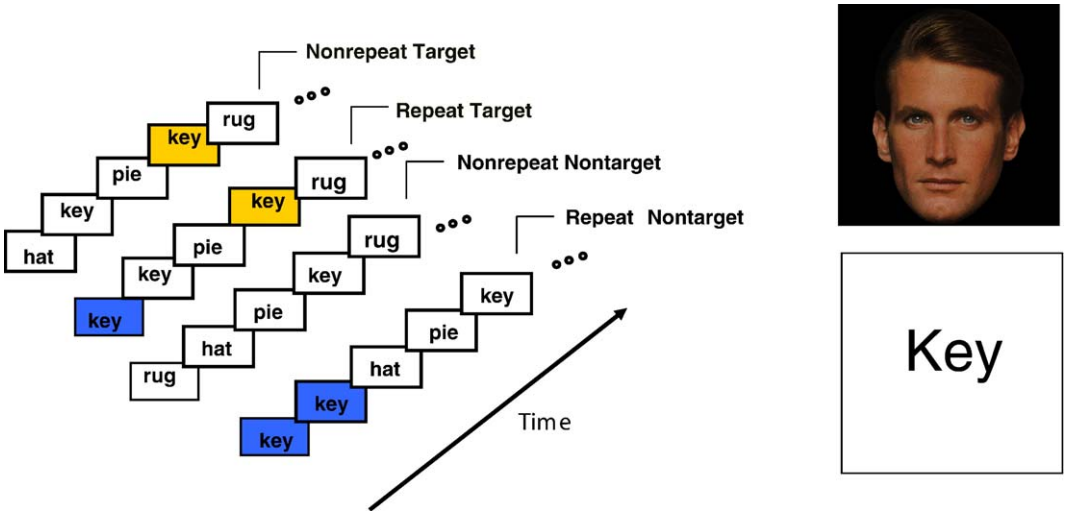

Fig. 1. 2back working memory paradigm used in the present study. Figure on the left represents the experimental design. Yellow boxes represent target items (items whose prior presentation was 2 trials ago). Blue boxes represent repeat items (items whose prior presentation was not in the correct 2back position). Figure on the right depicts examples of the word and face stimuli used in the present study.

compensate for rigid body motion (Ojemann et al., 1997); (4) intensity normalization to a whole brain mode value of 1000; and (5) spatial smoothing with an 8-mm FWHM Gaussian kernel. Functional data were transformed into stereotaxic atlas space (Talairach and Tournoux, 1988) by computing a sequence of affine transforms and resampled to 3 mm cubic voxels. Methods for movement correction and cross subject registration are analogous to the linear methods used in AIR (Woods et al., 1998).

2.3.2. Statistical analysis

2.3.2.1. Functional Magnetic Resonance Imaging Data (fMRI). For each participant, we estimated the magnitude of task-related activation in each voxel with a general linear model (GLM) using a box-car function convolved with a canonical hemodynamic response, with separate estimates for each material type (e.g., WM-words, WM-faces). These estimates were then entered into appropriately designed ANOVAs and *t*-tests (described below) that treated subjects as a random factor. We used significance and clustersize algorithms described in McAvoy, Ollinger and Buckner (2001) and Ollinger, Corbetta and Shulman (2001) to protect false-positive rates (21 contiguous voxels and a per-voxel alpha of .0001, corresponding to a corrected whole brain false positive rate of approximately .05).

To examine task related responses within each group, we computed paired sample *t*-tests comparing task and fixation for each stimulus type (word versus face) for each group separately. Our primary analysis approach for examining group differences was to conduct voxel-wise ANOVAs with group as a between-subject factor, and stimulus type (word, face) and condition (task, fixation) as within subject factors. First, we were interested in identifying regions that showed a group by condition interaction that did not further interact with stimulus type. These would be regions that demonstrated group differences in task-related activation with similar patterns for both word and face working memory. To identify such regions, we examined voxels showing group by condition interactions, but masked out voxels that further interacted with stimulus type. In addition, we were interested in identifying brain regions that showed a group by condition by stimulus type interaction. These are regions in which the group differences in task-related activity differed for word and face stimuli. In addition, we wanted to be sure that any regions identified as showing either of these interactions were ones in which there was a significant response to the task in at least one group, with at least one stimulus. Thus, we only examined voxels showing the interactions of interest if they demonstrated a significant difference between task and fixation in at least one group for either words or faces.

2.3.2.2. Behavioral data. Our version of the nback task was designed to assess the ability to code temporal order within the task by including repeat nontarget and target trials (see Fig. 1). Repeat nontarget trials, which we refer to as "lures" (Gray et al., 2003), are items whose prior presentation was not in the correct "2back" position. Rather, these items may have been presented one trial or three trials prior. Participants who have explicitly coded the temporal order of items should be able to recognize that prior presentation of the item was not in the correct 2back position and correctly reject such items as targets. Participants with deficits in temporal coding of items should be particularly likely to false alarm to such repeated non-targets (Perlstein et al., 2001) as they may be responding on the basis of familiarity to the repeated items rather than because they accurately encoded the item within WM. As another means of assessing the coding of temporal order in WM, we compared performance on two types of target trials: 1) nonrepeat target trials where the occurrence of the target item is only the second time the item was presented (e.g., prior presentation two trials back was the first presentation of the item); 2) repeat target trials where the target item has occurred more than twice (e.g., presented on a trial prior to the one two back). Participants who have explicitly coded the temporal order of items should not be influenced by prior presentation of targets items that were not in the correct nback position, and thus should not perform differently on nonrepeat and repeat targets. In contrast, participants who have difficulty with the temporal coding of items should actually benefit more from the familiarity trace of target items presented more than two times. To examine performance across these different trial types, the behavioral data (accuracy and RTs to correct trials) were analyzed using repeated measures ANOVAs with group as a between subject factor and stimulus type (word, face), target type (target, non-target) and repetition (repeated, non-repeated) as within subject factors.

3. Results

3.1. Behavioral data

The ANOVA for accuracy (Fig. 2) in the WM task indicated significant main effects of group [$F(2,105)=$

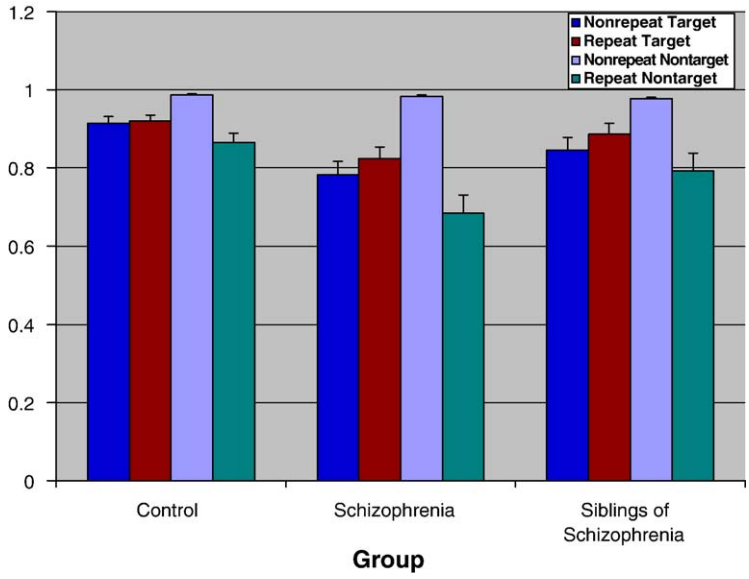

Fig. 2. Means and standard deviations of errors for the different working memory trial types.

11.1, $p<.001$], stimulus type [$F(1,105)=9.0$, $p=.003$], and repetition [$F(1,105)=56.0$, $p<.001$]. Post hoc comparisons using Tukey's honestly significant difference indicated that SCZ (82%) performed overall significantly worse than CON (92%). SIB (87%) performance levels fell between that of CON and SCZ but did not differ significantly from either group. All groups had more difficulties responding to face (93%) than word (96%) stimuli. Additionally, there was a target type by repeat interaction [$F(1,105)=64.8$, $p<.001$] that was further modified by a group by target type by repetition interaction [$F(1, 105)=5.6$, $p=.005$]. Planned contrasts to determine the source of this interaction demonstrated that all groups showed a significant target by repeat interaction (Fig. 2). However, effect sizes for SCZ (.67) and SIB (.40) were greater than those for CON (.25). In addition, analysis of repetition effects for targets only showed no significant

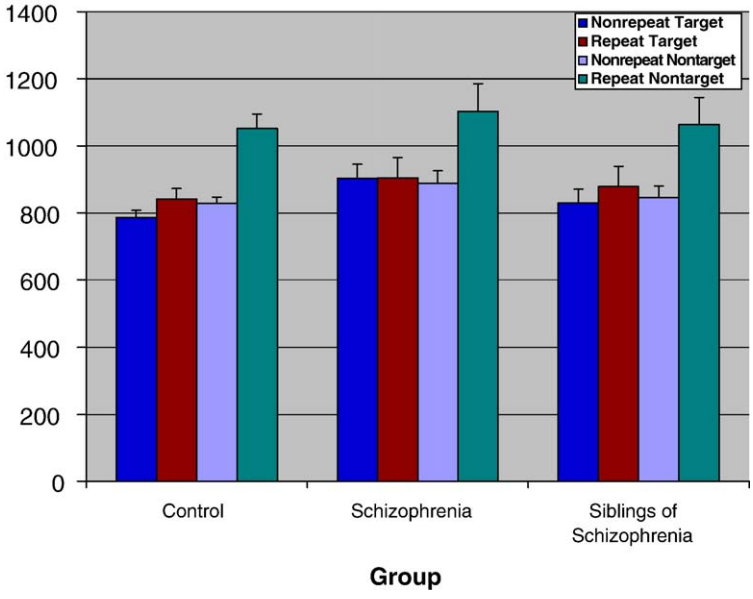

Fig. 3. Means and standard deviations of reaction times for the different working memory trial types.

differences between repeat and nonrepeat target trials in CON (Eta^2=.010), but a trend toward significance for SCZ (Eta^2=.15) and SIB (Eta^2=.15).

The ANOVA for reaction time (see Fig. 3) in the WM task indicated significant main effects of target type [$F(1,106)=31.6$, $p<.001$], and repetition [$F(1,106)=27.2$, $p<.001$]. There was also a target type by repetition interaction [$F(1,106)=43.4$, $p=.001$], but no group by target type by repetition interaction [$F(1,106)=.26$, $p=.769$]. All groups responded significantly faster to target (857 ms) than nontarget (963 ms) trials, and nonrepeat (846 ms) than repeat (974 ms) trials. Additionally, all groups responded more slowly to repeat nontarget trials (1073 ms) than to nonrepeat target (874 ms), repeat target (839 ms), and nonrepeat nontarget (853 ms) trials. There were no significant main effects of group or interactions with group.

3.2. fMRI data

Our first goal was to determine whether we elicited WM-related activity in regions consistent with those reported in the previous literature. Thus, we examined regions showing task-related activation within each group, separately for each stimulus type (word versus face). As shown in Fig. 4, all three groups demonstrated activation in regions classically associated with performance of WM tasks, including anterior cingulate cortex, and bilateral prefrontal cortex, parietal cortex, basal ganglia, thalamus and cerebellum. In addition, the patterns of activation as a function of material type were generally consistent with prior reports, with a large degree of overlap, but some evidence for right regions showing more face than word activation and left regions showing more word than face activation, particularly in prefrontal cortex.

Our second goal was to identify regions in which at least one of the groups showed task-related activity (collapsing across stimuli type) that was significantly different from one or both of the other groups. We predicted that there would be a set of regions where both SCZ and SIB showed altered task-related activity and another set that was altered in only SCZ. We first examined regions showing group (CON, SCZ, SIB) by condition (task, fixation) interactions. Such interactions reflect regions in which activity differed among the groups for both word and face WM. As shown in Table 2, consistent with our hypothesis, there were regions in parietal cortex and the nucleus accumbens in which *both* SCZ and SIB showed

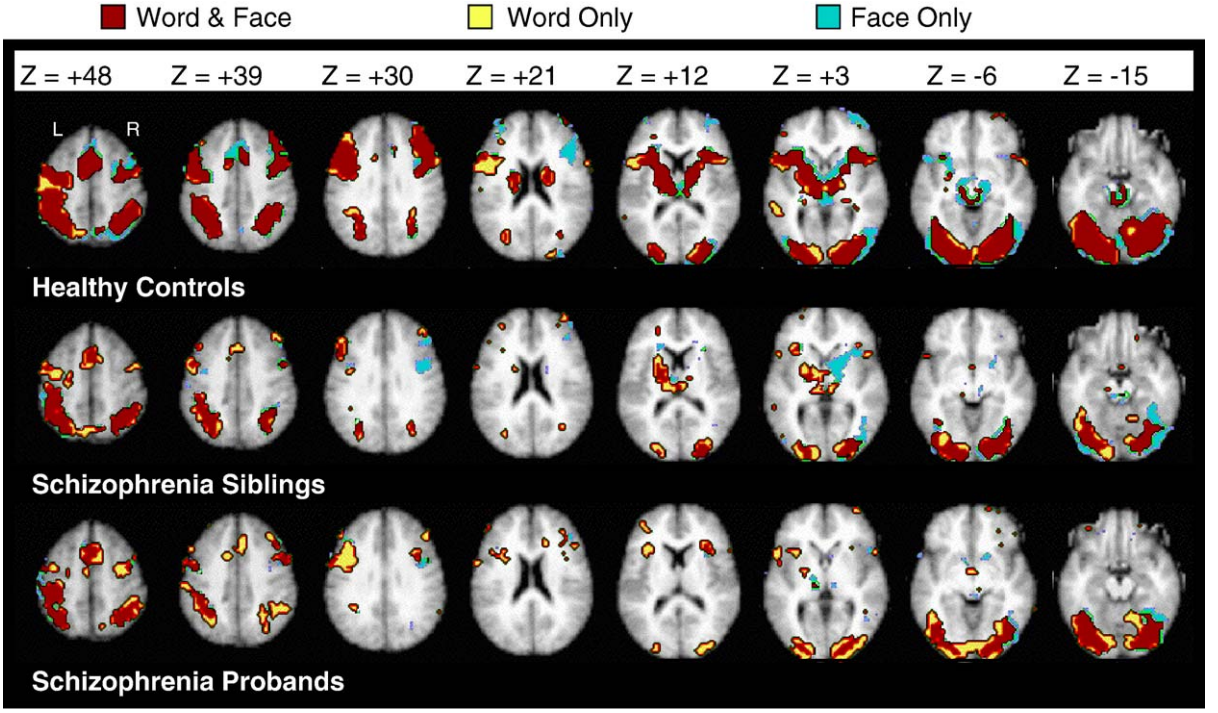

Fig. 4. Regions demonstrating significantly greater activation in task as compared to fixation within each group. Regions in red were active in both word and face working memory. Regions in blue were active in face working memory only, and regions in yellow were active in word working memory only.

Table 2
Regions showing group by condition interactions

Regions of Interest	Brodmann's areas	X	Y	Z	F value
SCZ = SCZ sibs > CON					
Right nucleus accumbens		+26	+0	−17	12.18
Left Parietal	7	−39	−65	+47	9.94
Left Parietal (somatosensory)	1/2	−26	−32	+67	10.97
SCZ > SCZ sibs = CON					
Right temporal	40/43	+55	−19	+21	10.13
Right cingulate	24	+04	−14	+37	6.82
Right motor	6	+04	−13	+55	6.96
Right motor	6	+11	−13	+70	13.70
SCZ < SCZ sibs = CON					
Left temporal	42	−61	−19	+10	7.96
SCZ sibs > SCZ > CON					
Right globus pallidus		+08	+04	+00	11.19

altered task-related activation compared to CON, but did not differ significantly from each other (as determined by posthoc contrasts). In all three regions, SCZ and SIB showed enhanced task related activity (Table 2 and Fig. 5). There were also several regions in which SCZ and SIB differed in their patterns of activity (Table 2 and Fig. 6). In the majority of these regions, SCZ showed enhanced task related activity compared to SIB and CON, though in the left temporal cortex, SCZ showed reduced activity compared to SIB and CON. Thus, these findings support our hypothesis that a subset of regions would show altered task-related activity in SCZ only.

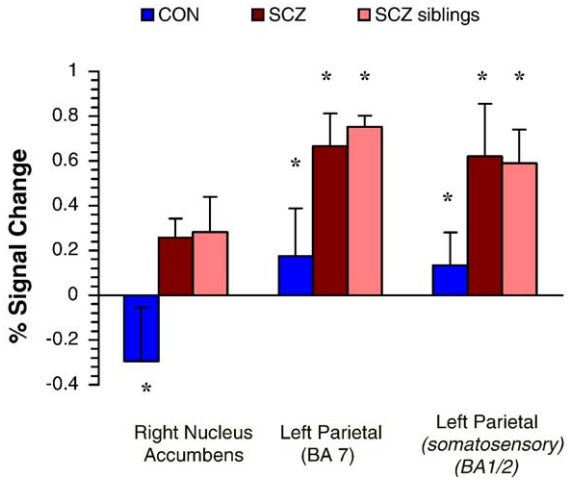

Fig. 5. Group differences in brain activity irrespective of stimulus type, such that individuals with schizophrenia (SCZ) and their siblings (SCZ siblings) have greater activation than controls (CON), but do not significantly differ from each other. Significant differences between task and fixation within each group are noted with asterisks. Standard errors are displayed.

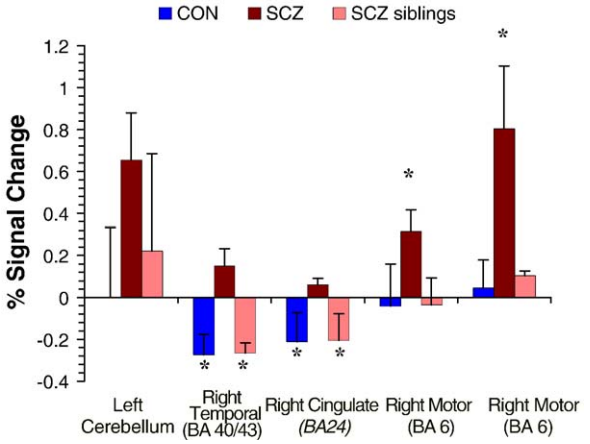

Fig. 6. Group differences in brain activity irrespective of stimulus type, such that individuals with schizophrenia (SCZ) and their siblings (SCZ siblings) significantly differ in their pattern of brain activity. Significant differences between task and fixation within each group are noted with asterisks. Standard errors are displayed.

Our third goal was to examine regions that demonstrated a significant group by condition by stimulus type interaction. Again, we predicted that there would be a subset of regions such that SCZ and SIB both showed altered task-related activity that differed across stimulus type and another subset of regions where only SCZ showed altered activity. To test the first hypothesis, we examined regions in which SCZ and SIB did not differ from each other (as determined by posthoc contrasts). As depicted in Table 3 and Fig. 7, there were a number of regions, including left parietal cortex and bilateral cerebellum, where SCZ and SIB showed greater task-related activity than CON for word stimuli but less activity than CON for face stimuli.

To test the second hypothesis, we then examined regions that also demonstrated a significant group by condition by stimulus type interaction, but where abnormal patterns of brain activity differed between SCZ and SIB in either or both of the word and face conditions. As can be seen in Table 4, the majority of these additional regions showed one of two different patterns, including 1) SCZ had greater activation than SIB and CON, who did not differ from each other; or 2) SIB had greater activation than both SCZ and CON, who did not differ from each other. Interestingly, regions in prefrontal cortex showed the first pattern, while regions in the cerebellum showed the second pattern (Fig. 7).

Table 3
Regions showing task by material effects such that activity in individuals with schizophrenia does not significantly differ from their siblings

Regions of interest	Brodmann's areas	X	Y	Z	F value	Group pattern for words	Group pattern for faces
Left cerebellum		−32	−54	−54	7.34	SCZ=SCZ sibs>CON	SCZ=SCZ sibs<CON
Right cerebellum		+28	−66	−33	11.3	SCZ=SCZ sibs>CON	SCZ=SCZ sibs<CON
Left cerebellum		−28	−72	−42	10.03	SCZ=SCZ sibs>CON	SCZ=SCZ sibs<CON
Left parietal	7	−02	−81	+45	13.02	SCZ=SCZ sibs>CON	SCZ=SCZ sibs>CON

3.3. Specificity to working memory

In the current study we compared a 2back WM condition to fixation, and did not have a parametric manipulation of load. Thus, it is possible that the abnormal activity in at least some of the regions is related to more general cognitive processing recruitments that might be needed in a range of cognitive tasks, rather than being specifically related to WM. To help address this concern, we examined the activity in the brain regions identified in WM during incidental encoding tasks that the same subjects performed as a part of a different paradigm during the same scanning session (Bonner-Jackson et al., in press) with the same imaging parameters. These encoding tasks did not require any WM load, but did require visual processing, decision-making and response selection and execution. There was a verbal incidental encoding task (semantic processing, with participants required to judge whether each of a series of words was abstract or concrete) and a face task (gender judgments).

For the 9 regions identified as showing a group by condition effect (Table 2), we examined whether these patterns interacted with task, using 3 way ANOVAs in each ROI with condition (task, fixation), task (WM, encoding) and diagnostic group as factors. Three of the 9 regions showed a significant group by condition by task interaction ($p<.05$) and did *not* show a significant group by condition interaction when just the encoding data was examined ($p>.08$). These regions included

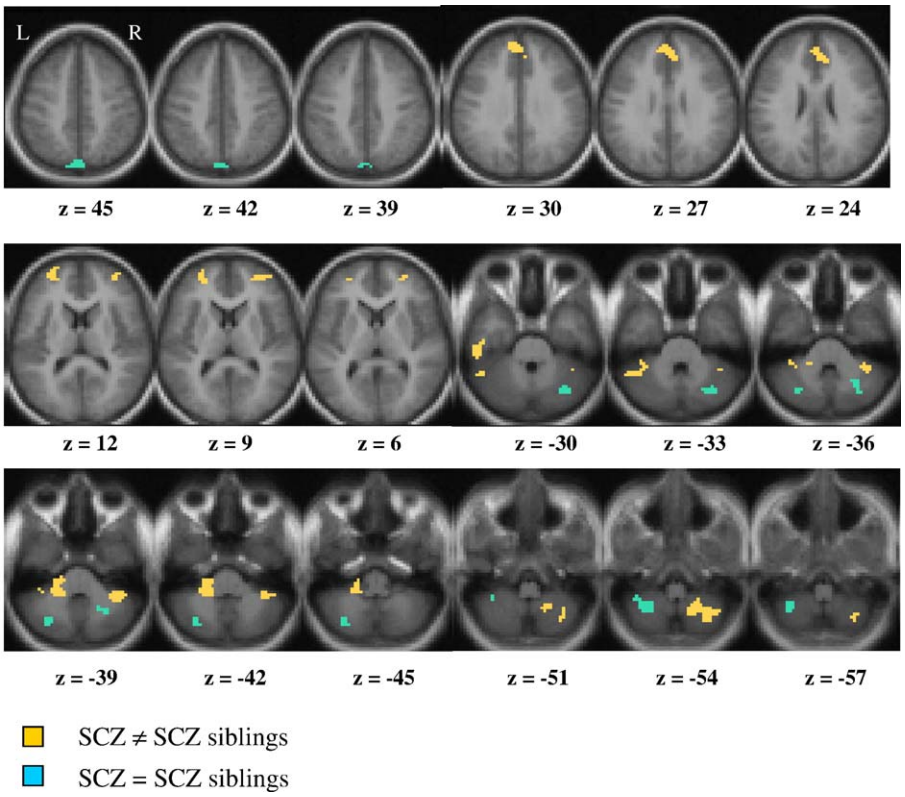

Fig. 7. Group differences in brain activity as a function of stimulus type (blue=regions where activity did not significantly differ between individuals with schizophrenia and their siblings; yellow=regions where activity did significantly differ between individuals with schizophrenia and their siblings).

Table 4
Regions showing task by material effects such that activity in individuals with schizophrenia significantly differs from their siblings

Regions of interest	Brodmann's areas	X	Y	Z	F value	Group pattern for words	Group pattern for faces
Left prefrontal	10/46	−26	+51	+09	8.74	SCZ>SCZ sibs=CON	SCZ<SCZ sibs=CON
Left prefrontal	9	−02	+42	+27	9.81	SCZ>SCZ sibs=CON	SCZ<SCZ sibs=CON
Right prefrontal	10/46	+32	+51	+09	6.92	SCZ>SCZ sibs>CON	SCZ=SCZ sibs<CON
Right cerebellum		+26	−60	−54	8.16	SCZ sibs>SCZ=CON	SCZ sibs<SCZ=CON
Left cerebellum		−40	−48	−33	8.47	SCZ sibs> SCZ=CON	SCZ sibs< SCZ=CON
Right cerebellum		+38	−45	−39	10.12	SCZ sibs>SCZ=CON	SCZ sibs<SCZ=CON
Left cerebellum		−20	−39	−42	8.40	SCZ sibs>SCZ=CON	SCZ=SCZ sibs=CON

right nucleus accumbens (+26, 0, −17), right temporal cortex (+55, −19, +21), and left parietal (−39, −65, +55). The globus pallidus region (+8, +4, 0) and one of the motor regions (+11, −13, +70) also showed a significant group by condition by task interaction, but *did* show a group by condition interaction in the encoding data alone ($p<.01$). In these regions the group differences were similar in WM and encoding, but was amplified in WM. For the remaining four regions (left temporal, cingulate, motor and left parietal) group differences were the same in pattern and magnitude in both WM and encoding. Ten of the 11 regions showing group by condition by stimulus interactions (Table 3) demonstrated further interactions with task (WM versus encoding; all $ps<.05$) and did *not* show significant group by condition by stimulus interactions in the encoding data alone (all $ps>.10$). Only one cerebellar region (−29, −71, −42) did *not* show a significant interaction with task ($p>.4$), but also did not show a significant group by condition by stimulus interaction in just the encoding data. Thus, these data suggest that the altered activation patterns among individuals with schizophrenia and/or their siblings in many of these brain regions are specific to or augmented by WM demands, but that altered activity in some regions may reflect abnormalities in non-WM specific processes.

3.4. Effects of task performance and gender

A potential interpretative issue in cognitive imaging studies is that differences in task-related brain activation among groups may reflect differences in performance levels. Thus, we examined task-related activation in a subset of the participants (55 CON, 10 SCZ, 14 SIB) that were matched on accuracy levels. The vast majority of brain regions that showed group differences in the full sample continued to show the same group differences in the samples matched on performance levels. In the right globus pallidus (+08, +03, +00), there was no longer a significant difference between SCZ and SIB, although they both still showed significantly greater activation than CON. Within left temporal cortex (−62, −18, +09), the pattern of activity changed from SCZ showing significantly less activity than SIB and CON, to showing significantly greater activity compared to both groups. Another potential confound in the current study is that a larger percentage of the probands with schizophrenia were males than either their siblings or controls. To address this question, we redid the analysis including gender as a factor. All effects of group that were significant in the full sample analysis remained significant.

4. Discussion

The primary goal of the present study was to examine WM and functional brain activation differences in SCZ and their siblings who were still within the age of risk for developing the disorder. Consistent with previous studies assessing WM performance in SCZ (Barch et al., 2001; Carter et al., 1998), SCZ had both impaired performance and activation. The behavioral data suggested that SCZ were particularly likely to incorrectly respond to repeated non-targets, but benefited from repetition of target stimuli. This suggests that SCZ were having difficulty coding the temporal order of items within WM. The SIBs showed a very similar behavioral pattern, though their level of impairment was intermediate between their ill siblings and CON. These findings differ somewhat from a previous study that reported equal performance levels on an nback task in SIBs and CONs (Callicott et al., 2003a), but are consistent with other work showing impaired nback performance in SIBs (Goldberg et al., 2003).

To our knowledge, this is the first study to directly compare functional brain activation in SCZ and SIB using *both* word and face assessments of WM. As discussed above, prior studies of brain activation in SIBs have reported discrepant results, perhaps due to differences in the age of the sample or differences in the stimulus type (i.e., word or face). In the current study, there were a number of regions within PFC in

which SCZ showed altered task-related activity compared to SIB and CON. SCZ demonstrated *increased* task-related activation compared to SIB and CON for word stimuli, but *decreased* task-related activation in comparison to SIB and CON for face stimuli in left PFC. In right PFC, both SCZ and SIB showed increased task-related activation in comparison to CON, but decreased task-related activation for face stimuli. These results suggest that PFC dysfunction during WM performance in SCZ and SIB may vary according to the stimulus type (i.e., word versus face). However, differences in activation related to stimulus type could also reflect varying task difficulty, as the face WM task was more difficult than the word WM task for all participants. Notably, post-hoc examination of task-related activation in a subset of the SCZ and SIB groups that had similar performance on word and face WM found the same pattern of differential PFC activation as a function of stimulus type. We should also note that the regions with altered PFC activity that we found were not in dorsolateral PFC proper, but in more anterior PFC regions (BA 10) or in more medial aspects of BA 9. An alternative explanation is that the two conditions require different strategies that may interact with brain function. For example, it may be that SCZ show enhanced activity during verbal WM in some PFC regions because they may be trying to bring to bear compensatory processing that may be more easily utilized with word than face materials. Future studies utilizing word and face working memory tasks matched for task difficulty a priori could be used to further explore the relationship between strategy use and brain function in individuals at risk for schizophrenia.

Another goal of the present project was to determine whether differences in brain activation during WM tasks might extend to regions other than the PFC. Consistent with the literature, our results demonstrated functional abnormalities in SCZ within cerebellar and parietal regions. The SIBs had many of the same patterns of dysfunction within cerebellar and parietal regions as did their ill siblings. For example, SCZ and SIB both demonstrated increased task-related activity within bilateral cerebellar and left parietal regions that varied *as a function of* stimulus type. These regions demonstrated *increased* task-related activity for SCZ and SIB in comparison to CON for word stimuli, but *decreased* task-related activity for face stimuli. Hyperactivation in parietal cortex in young high-risk relatives during a verbal working memory task is consistent with findings by Whalley et al. (2004) who found increased left parietal activity in high-risk relatives during completion of a Hayling sentence completion paradigm. Differences in the pattern of cerebellar activation as a function of task type may reflect the cerebellum's involvement with the sequencing of words and phrases (Ackermann et al., 2004). It is possible that hyperactivation of certain cerebellar regions in SCZ and SIB may reflect a compensatory mechanism, such that additional areas are recruited in order to complete task demands. We did not predict the nucleus accumbens results a priori. However, hyperactivation in this region is consistent with a previous study that found activation in the basal ganglia that was absent in controls (Manoach et al., 2000). In addition, previous studies using animal models have found increased activity of D2 receptors in the striatum (Kellendonk et al., 2006), which then influences PFC function. However, the exact nature of the relationship between the striatum and PFC is still unclear. Overall, these findings provide further evidence that disturbances in a distributed neural circuit involving both cortical and subcortical regions may underlie disturbances in the ability to encode the temporal order of items in WM tasks in schizophrenia.

Findings of changes in task-related brain activation that are similar in both SCZ and SIB provide important information about functional abnormalities that may be associated with the genetic vulnerability to developing schizophrenia. However, differences in functional brain activation between SCZ and SIB can provide clues as to which abnormalities are necessary to manifest the illness, or which abnormalities are influenced by medication status or other disease-related factors. As discussed above, some regions of the cerebellum showed different patterns of activation between SCZ and SIB, while other regions showed similar patterns. One possible explanation for such findings is that subregions within the same brain region have different functional roles in WM and thus may be differentially associated with vulnerability versus manifest illness. For example, the posteriorlateral cerebellum tends to be involved with higher cognitive functions and is activated during language tasks independent of movement (Gebhart et al., 2002), while less posterior regions of the cerebellum tend to be activated during the execution (Hanakawa et al., 2003) or imagining (Decety et al., 1994) of motor movements. In the current study, the cerebellar regions impaired in both SCZ and SIB tended to be in the posteriorlateral section, while the regions whose activity differed between SCZ and SIB tended to be less posterior.

There were several limitations in the current study. First, the present study did not include 0back and 1back conditions in addition to the 2back condition of the nback. However, to determine whether the disturbances

in brain activation that we found in SCZ and SIBS were specific to WM or associated with more general cognitive processing demands, we compared patterns of activity from the present study to that of another study in our lab that used an episodic encoding task. In five of the nine regions (right nucleus accumbens, right temporal cortex, left parietal cortex, globus pallidus and right motor cortex), the group differences were significantly greater in WM as compared to episodic encoding, and three of the nine regions showed no group differences in encoding. This suggests that these regions are involved more specifically with WM processes. In contrast, left temporal cortex, cingulate, a more inferior parietal region and a more inferior motor region demonstrated similar group differences in WM and encoding, suggesting involvement with cognitive processes engaged by a range of cognitive tasks. Further, in regions showing a group by condition by stimulus interaction, the effects were specific to WM and significantly different in WM in all but one region. A second limitation was that all of the SCZ were taking medications. As such, we could not rule out the possibility that differences between SCZ and SIB were due to medications as opposed to disease status. However, there were a number of regions that showed task-related functional brain activation changes in both SCZ and SIB. Given that the SIB were not taking any medications, disturbances in these regions cannot be attributed to medication effects. A third limitation was that the SCZ group had a larger percentage of males than either SIB or CON. However, gender only interacted with group in one region. Further, SIB and CON did not differ in the percentages of males. Thus, differences between SIB and CON are not confounded by the potential influence of gender.

To summarize, this study demonstrated clear changes in WM performance and associated brain activation in both SCZ and SIB. Our findings provide further evidence that impairments in WM associated with abnormalities of related brain regions are associated with genetic vulnerability to schizophrenia. There were also regions, predominantly in PFC and cerebellum, where the pattern of activity varied for word or face stimuli. In order to further our understanding of the relationship between cognition, brain activation, and the underlying neurobiology of schizophrenia, future studies should examine the nature of PFC and other cortical dysfunction as a function of WM domain in individuals with the usual form of schizophrenia as well as those who may have the cognitive deficits associated with schizophrenia but not the psychotic symptoms associated with the usual form of the disorder.

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