Levels-of-Processing Effects in First-Degree Relatives of Individuals with Schizophrenia

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Background: First-degree relatives of individuals with schizophrenia show cognitive impairments that are similar to but less severe than their ill relatives. We have shown that memory impairments can be improved and prefrontal cortical (PFC) activity increased in individuals with schizophrenia by providing beneficial encoding strategies. The current study used a similar paradigm to determine whether siblings of individuals with schizophrenia (SIBs) also show increases in brain activity when presented with beneficial encoding strategies.

Methods: Twenty-one SIBs and 38 siblings of healthy comparison subjects underwent functional magnetic resonance imaging scans while engaged in deep (abstract/concrete judgments) and shallow (orthographic judgments) encoding. Subjects were then given a recognition memory test.

Results: The groups did not differ on encoding or recognition accuracy, and the SIBs benefited from deep encoding to a similar degree as control subjects. The SIBs showed deep encoding-related activity in a number of PFC regions typically activated during semantic processing. However, SIBs showed more activity than control subjects in three subregions of PFC (left BA 44 & BA 47 bilaterally).

Conclusions: Siblings of individuals with schizophrenia benefit from supportive verbal encoding conditions. Like individuals with schizophrenia, SIBs also show increased task-related activity in a larger number of PFC subregions than control subjects during deep verbal encoding.

There is consistent evidence of a significant genetic component to schizophrenia (Gottesman 1991; Tsuang et al. 1991, 1999). In support of this genetic involvement, first-degree relatives of individuals with schizophrenia show neuropsychological impairments that are similar to but less pronounced than those found in individuals with schizophrenia (Cannon et al. 1994; Hughes et al. 2005; Keefe et al. 1994; Krabbendam et al. 2001).

Verbal memory dysfunction represents one of the most pronounced cognitive deficits in individuals with schizophrenia (Cirillo and Seidman 2003), and a rapidly growing literature has identified similar verbal memory impairments in the first degree relatives of individuals with schizophrenia (Kremen et al. 1994; Sitskoorn et al. 2004; Snitz et al. 2006). For example, a recent meta-analysis by Sitskoorn et al. (2004) identified verbal memory functioning as one of the most reliable ways to differentiate between unaffected relatives of individuals with schizophrenia and control subjects. Thus, deficits in verbal memory might represent one neurocognitive indicator of risk for schizophrenia.

Relatively little is known about the alterations in brain activation associated with verbal episodic memory deficits in the relatives of individuals with schizophrenia. Studies of schizophrenia subjects have typically found abnormal encoding-related brain activity in conjunction with impaired task performance (Barch et al. 2002; Crespo-Facorro et al. 1999; Heckers et al. 1998; Jessen et al. 2003; Ragland et al. 2004; Weiss et al. 2003). In general, individuals with schizophrenia show an atypical pattern of activation in frontal and medial temporal lobe regions during episodic memory encoding.

Although neuroimaging studies have examined working memory-related brain activity in unaffected relatives of individuals with schizophrenia (Callicott et al. 2003; Seidman et al. 2006; Thermenos et al. 2004), there have been few studies of episodic

memory in this group. One such study (Whyte et al. in press) found over-activation of right IFG and right cerebellum during episodic memory processing in a group of individuals at high risk for the development of schizophrenia. Further research in this area would provide greater insights into the neural substrates of verbal episodic memory in individuals with an elevated genetic risk for schizophrenia, while avoiding some of the pitfalls that typically confound research with actively ill participants (medication, performance effects, etc.).

A paradigm often used for studying verbal memory is the levels-of-processing paradigm (Craik and Lockhart 1972). In this paradigm, participants are oriented to process stimuli to different degrees (e.g., semantically vs. orthographically) at encoding and are then given a subsequent memory test. "Deep" encoding is very often, although not always, associated with better recall and recognition than "shallow" encoding (Craik and Lockhart 1972; Craik and Tulving 1975) and has been shown to preferentially activate areas in left prefrontal cortex (PFC), particularly the left IFG (Casasanto et al. 2002; Fletcher et al. 2003; Kapur et al. 1994; Otten and Rugg 2001; Otten et al. 2001). Our group (Bonner-Jackson et al. 2005) and others (Ragland et al. 2003, 2005) have recently found that individuals with schizophrenia, like healthy control subjects, benefit from deep encoding of words and show encoding-related cortical activity in typical semantic processing regions (e.g., L BA 47) when using deep processing strategies. However, our findings indicated that even when supported by beneficial verbal encoding strategies, the schizophrenia subjects activated regions of PFC not activated by the control group, including the left inferior frontal (BA 45), right inferior frontal (BA 45), and left middle frontal gyrus (BA 10). It is still unclear, however, whether this expanded pattern of cortical activity during verbal episodic memory performance is related to the schizophrenia disease process or associated with the underlying genetic risk for development of the disease. If the latter possibility were true, then unaffected first-degree relatives of individuals with schizophrenia should show a similar pattern of expanded prefrontal cortex activity during deep verbal episodic memory encoding.

The goal of the current study was to test the hypothesis that first-degree relatives of individuals with schizophrenia: 1) show memory benefits after a levels-of-processing manipulation; 2) acti-

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vate typical semantic processing regions during deep encoding, including left IFG (BA 47); and 3) show a pattern of expanded bilateral PFC activity during deep encoding.

Methods and Materials

Participants

The participants were 24 siblings of DSM-IV–diagnosed schizophrenia subjects (SIBs) and 40 siblings of healthy comparison subjects (SNCs). All participants were recruited to participate in studies of brain structure and function at the Conte Center for the Neuroscience of Mental Disorders at Washington University. Potential participants were excluded for any of the following: 1) meeting DSM-IV criteria for substance abuse or dependence within the past 3 months, 2) the presence of any clinically unstable or severe medical disorder, 3) head injury with documented neurological sequelae or loss of consciousness, or 4) meeting DSM-IV criteria for mental retardation (mild or greater in severity). Demographic information is displayed in Table 1 and is limited to the subjects who had valid neuroimaging data. Data from 5 participants (3 SIBs, 2 SNCs) were unusable because of excessive movement during scanning (i.e., movement greater than 2 SDs above the mean in the X, Y, or Z plane) and poor signal-to-noise ratios. Thus, all data presented are for 21 SIBs and 38 SNCs. The SNCs and SIBs were statistically similar on all variables, including gender composition, and exclusion of the participants with invalid neuroimaging data did not alter the results of the between group comparisons.

Diagnostic information was collected by a specially-trained MSW-level research assistant with the Structured Clinical Interview for DSM-IV (SCID-IV; Spitzer *et al*. 1990), the Structured Interview for Prodromal Syndromes (Miller *et al*. 1999), and all available hospital records and corroborative family sources. Mean ratings for positive, negative, disorganized, and general symptoms are displayed in Table 1. Although ratings for SIBs were higher than those of SNCs on all four scales, none of the differences reached statistical significance. However, in other work with a larger sample size, the SIBs scored significantly higher than SNCs on negative symptoms (Delawalla *et al*. 2006).

Written informed consent was obtained for all participants before participation in any aspect of the research. All experimental procedures were approved by the Institutional Review Board (IRB) of Washington University in St. Louis and complied with these regulations.

Table 1. Demographic and Clinical Data

Characteristic	SCNs	SIBs
Age (yrs)	20.9 (3.5)	21.1 (3.5)
% Male	26.3	47.6
Parents' Education (yrs)	15.3 (2.4)	14.6 (2.9)
Education (yrs)	13.1 (2.4)	12.9 (2.8)
Handedness (% right)	83.3	84.2
SIPS – Positive (Sum)	.67 (1.6)	1.3 (2.4)
SIPS – Negative (Sum)	.72 (1.7)	1.5 (3.3)
SIPS – Disorganized (Sum)	.61 (1.3)	.76 (1.1)
SIPS – General (Sum)	1.5 (2.8)	2.1 (3.0)

Data presented as mean (SD).

SCNs, siblings of control subjects; SIBs, siblings of participants with schizophrenia; SIPS, Structured Interview for Prodromal Syndromes; data for 2 SCNs was unavailable.

Tasks and Materials

The tasks and materials used were identical to those described elsewhere (Bonner-Jackson *et al*. 2005). Briefly, all subjects performed encoding and recognition tasks while being scanned. Participants saw 64 words in each of the two scanning runs (128 words total). Participants made deep encoding (abstract/concrete) judgments in one scanning run and shallow encoding (orthographic) judgments in the other scanning run. During the recognition task, subjects were presented with 64 words and made yes/no responses to indicate whether or not they had seen the current word during either of the encoding tasks. One-half of the words presented at recognition were old (equal numbers from deep and shallow encoding) and one-half were new foils. Foils were matched with targets on word length and frequency. Not all words presented during encoding were assessed at recognition. The encoding tasks always took place before the recognition task, but task order for shallow and deep encoding was counterbalanced across participants.

Stimuli for the verbal tasks were visually presented words, 3–10 letters in length, and presented in 48-point Geneva font, as previously reported (Barch *et al*. 2002; Braver *et al*. 2001; Kelley et al 1998; Logan *et al*. 2002; McDermott *et al*. 1999).

Participants performed tasks in runs lasting 4.25 min each. Runs included four task blocks of 16 trials each and three fixation blocks of 10 trials each interleaved in alternating order with the task blocks. Additionally, four fixation trials at the beginning were discarded in the analysis of the data (used to allow magnetic resonance signal to reach steady state) and there were four additional fixations at the end. Task blocks lasted 40 sec, and fixation blocks lasted 25 sec. Each of the items in a task block was presented for 2 sec followed by a 500-msec interstimulus interval. During fixation blocks, a cross hair appeared continuously and participants were instructed to fixate.

Outside of the scanner, all participants received a battery of neuropsychological tests, including measures of episodic memory function (e.g., Logical Memory, Family Pictures, and the California Verbal Learning Test).

Scanning

All scanning was performed on the 1.5T Siemens VISION system (Siemens, Malvern, Pennsylvania). Functional images were collected with an asymmetric spin-echo echo-planar sequence sensitive to blood oxygenation level-dependent (BOLD) contrast (T2*) (repetition time [TR] = 2500 msec, echo time [TE] = 50 msec, field of view = 24 cm, flip = 90°). During each functional run, 102 sets of axial images were acquired parallel to the anterior–posterior commissure plane (3.75×3.75 mm in-plane resolution), allowing complete brain coverage at high signal-to-noise ratio (Conturo *et al*. 1996). Nineteen slices 7 mm thick were acquired in each image. Structural images were acquired with a coronal magnetization-prepared rapid gradient-echo imaging (MPRAGE) three-dimensional T1-weighted sequence (TR = 9.7 msec, TE = 4 msec, flip = 10°; voxel size = $1 \times 1 \times 1.2$ mm) and used for between-subject registration (as described in the following section) and anatomic localization.

Data Analysis

Functional Magnetic Resonance Imaging Data. Functional magnetic resonance imaging preprocessing included: 1) compensation for slice-dependent time shifts, 2) elimination of odd/even slice intensity differences due to interpolated acquisition, 3) realignment of all data acquired in each subject within and across runs to compensate for rigid body motion (Ojemann

Table 2. Behavioral Data: Encoding and Recognition of Words

Task	Measure	SCNs	SIBs
Word Encoding (Deep)	Accuracy	.80 (.08)	82 (.08)
	Reaction Time (ms)	992 (142)	1056 (124)
Word Encoding (Shallow)	Accuracy	.95 (.04)[a,b]	.91 (.09)[a]
	Reaction Time (ms)	1022 (134)	1049 (145)
Word Recognition (New)	% Correct Rejections	.72 (.30)	.69 (.31)
	Reaction Time (ms)	1063 (164)	1026 (154)
Word Recognition (Deep)	Accuracy	.60 (.29)[c]	.51 (.39)[c]
	Reaction Time (ms)	1018 (195)	1008 (183)
Word Recognition (Shallow)	Accuracy	.33 (.29)	.26 (.46)
	Reaction Time (ms)	1086 (210)[d]	1078 (133)[d]

Data presented as mean (SD). Abbreviations as in Table 1.
Corrected Hit Rates (Hits – False Alarms) are reported for Recognition accuracy data.
[a]Main effect of encoding depth (Shallow > Deep), $p < .001$.
[b]Group $\times$ Depth interaction (SCNs > Siblings of Probands).
[c]Main effect of encoding depth for recognition accuracy (Deep > Shallow), $p < .001$.
[d]Main effect of encoding depth for recognition RT (Shallow > Deep), $p < .001$; (Shallow > New), $p < .05$.

et al. 1997), 4) intensity normalization to a whole brain mode value of 1000, and 5) spatial smoothing with an 8-mm full-width-at-half-maximal Gaussian kernel. The functional data were transformed into the stereotaxic atlas space of Talairach and Tournoux (1988) by computing a sequence of affine transforms (first frame echo-planar imaging [EPI] to T2-weighted turbo spin echo [TSE] to MPRAGE to atlas representative target) composed by matrix multiplication. All analyses described in the following section were conducted on the basis of atlas-transformed data resampled to 3-mm cubic voxels.

For each participant, we estimated the magnitude of task-related activation in each voxel with a general linear model (GLM) and a boxcar task function convolved with a Boynton hemodynamic response function, with separate estimates for each encoding task. These estimates were then entered in appropriately designed analyses of variance (ANOVAs) and *t* tests (described in more detail in the following) that treated subjects as a random factor. To control for false-positive rates, we used a cluster-size threshold of 9 contiguous voxels and a per-voxel α of at least .0004, corresponding to a corrected whole brain false positive rate of approximately .05. We required multiple effects to be significant simultaneously, a *p* value threshold of .02 being required for each effect and resulting in a combined significance of either .0004 (.02 $\times$ .02) or .000008 (.02 $\times$ .02 $\times$ .02) (Barch *et al.* 2001).

We examined group differences in brain regions sensitive to levels-of-processing. To identify task-responsive regions for the levels-of-processing effect that also showed group differences, we required voxels to show all of the following: 1) significant task-related activation for either deep or shallow word encoding task for either SCN or SIB, with voxel-wise dependent sample *t* tests; 2) greater task-related activity for either deep encoding compared with shallow or for shallow compared with deep encoding, in either the SCN or SIB group, with voxel-wise within subject *t* tests; and 3) significant group differences in encoding task-related activation, with voxel-wise ANOVAs with group (SCN, SIB) as a between-subject factor and encoding depth (deep, shallow) as a within-subject factor.

Behavioral Data. Accuracy and mean reaction times (RTs) for correct responses were examined for encoding and recognition tasks separately with ANOVAs and *t* tests. Recognition responses were classified as "hits" if subjects correctly identified previously seen words and as "correct rejections" when subjects correctly identified new words.

Results

Behavioral Data

Encoding Performance. Encoding performance data were analyzed with repeated measures ANOVAs with Group (SCN, SIB) as the between-subjects factor and Depth (deep, shallow) as the within-subjects factor (Table 2). The ANOVA for encoding accuracy revealed a main effect of task type [$F(1,57) = 107.93$, $p < .001$]. Post hoc contrasts revealed significantly better performance on the shallow (M = .93) than the deep (M = .81) task within each group ($p < .001$). The Group $\times$ Depth interaction was also significant [$F(1,57) = 4.78$, $p < .05$]. Post hoc analyses revealed that SNCs (M = .95) performed the shallow encoding task significantly better than SIBs (M = .91), [$t(57) = 2.21$, $p < .05$], whereas performance of the deep encoding task did not differ between the groups ($p > .5$). The ANOVA for RT did not reveal any significant effects.

Recognition Performance. The recognition accuracy data were analyzed with a 2 $\times$ 2 ANOVA, with Group (SCN, SIB) as the between-subjects factor and Depth (deep encoding, shallow encoding) as the within-subjects factor (see Table 2). Corrected hit rates (hits $-$ false alarms) were computed for the deep and shallow recognition conditions analyzed in the ANOVA. The ANOVA for recognition accuracy revealed a significant main effect of encoding depth [$F(1,57) = 66.92$, $p < .001$]. Post hoc comparisons revealed that corrected hit rates for deeply encoded words (M = .57) were significantly higher than those for shallowly encoded words (M = .30). Neither the effect of Group ($p > .35$) nor the Group $\times$ Depth interaction ($p > .81$) was significant.

The recognition RT data were analyzed with a 2 $\times$ 3 ANOVA, with Group (SCN, SIB) as the between-subjects factor and Depth (deep encoding, shallow encoding, new) as the within-subjects factor. The ANOVA revealed a main effect of encoding depth [$F(2,56) = 9.56$, $p < .001$]. Post hoc comparisons revealed that recognition RT was significantly longer for shallowly encoded words (M = 1083) than for deeply encoded words (M = 1014) [$t(58) = 4.5$, $p < .001$]. Additionally, recognition RT was significantly longer for shallowly encoded words than for new words (M = 1050) [$t(58) = 2.02$, $p < .05$], with trend-level significant differences between deeply encoded words and new words ($p = .068$). No other significant differences were obtained.

Neuropsychological Measures. Neuropsychological data from 2 SIBs and 2 SNCs were not available. Data presented here are based on 19 SIBs and 36 SNCs, and group means are

Table 3. Neuropsychological Data

	SCNs	SIBs	Effect Size (d)
Logical Memory I (Scaled)	11.4 (2.9)	9.9 (3.7)	.4512
Family Pictures I (Scaled)	11.4 (2.8)[a]	9.2 (2.2)	.8737
CVLT: Short Delay Free			
Recall (Raw)	12.8 (2.1)	12.1 (1.9)	.3495

Data presented as mean (SD). CVLT, California Verbal Learning Test; other abbreviations as in Table 1.

[a]SCN > SIB ($p < .005$).

presented in Table 3. The SIBs, as compared with SNCs, demonstrated deficits on one measure of nonverbal episodic memory [Family Pictures 1, $t(53) = 3.06$, $p < .005$]. No other significant differences between groups were detected.

Neuroimaging Data

We began our analysis of the neuroimaging data by identifying brain regions within each of the groups (SCN, SIB) that showed levels-of-processing effects (i.e., greater task-related activity during deep encoding than shallow encoding or greater task-related activity during shallow than deep encoding; see Methods and Materials for analysis details). Regions of significant activity are displayed in Table 4.

As has been found in previous studies, SNCs showed greater activity in deep rather than shallow in typical semantic encoding regions, including left inferior frontal (BA 47) and superior frontal (BA 6) gyrus. For the same contrast, SIBs showed activity in similar semantic processing regions, including left inferior frontal (BA 44/47) and middle frontal (BA 6) gyrus. However, SIBs also showed deep encoding-related activity in areas of right IFG (BA 44/47; Table 4, Figure 1).

Next, we examined regions that demonstrated significant between-group differences (SCN > SIB or SIB > SCN) in the levels-of-processing effect (see Methods and Materials for details of analysis procedure). As shown in Figure 2, this analysis revealed three regions of significant between-group differences: one in right IFG (BA 47) and two in left IFG (BA 44 & 47). Post hoc analyses revealed that in all three regions SIBs demonstrated significantly more activity during deep than during shallow encoding (all p values < .02), whereas SNCs showed no significant differences between deep and shallow encoding in these regions (all p values > .15). In addition, SIBs demonstrated
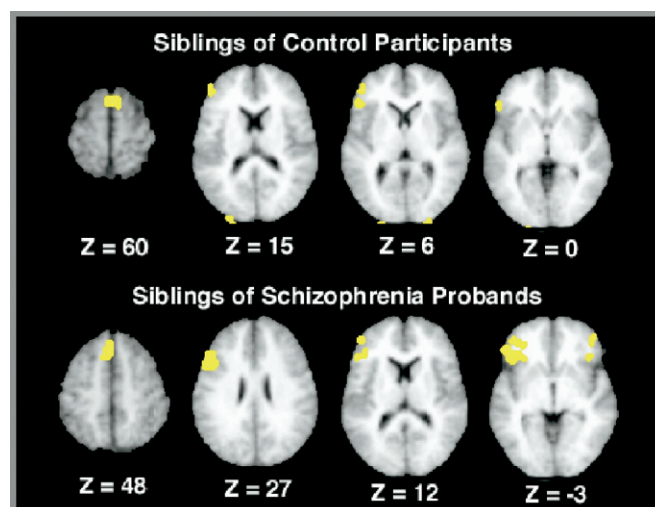

Figure 1. Levels-of-processing effect (deep > shallow encoding) for siblings of control participants (top) and siblings of individuals with schizophrenia (bottom). Both groups demonstrated intact levels-of-processing effects in typical semantic processing regions, including left IFG (BA 47). In addition, siblings of individuals with schizophrenia showed additional activation not seen in control subjects in right IFG (BA 44/47), among other regions. (Note: Right side of image represents right side of brain, left side of image represents left side of brain.)

significantly greater task-related activity during deep encoding than SNCs in each of these three regions.

We next investigated the effect of encoding task performance on cortical activity in the three regions that showed significant between-group differences for the deep > shallow encoding contrast (R BA 47, L BA 47, L BA 44). To do this, we correlated task performance during deep encoding with mean activation values during deep encoding in the three regions of interest (ROIs) in each group separately. In SNCs, the activity in the three regions did not correlate significantly with deep encoding task performance (all p values > .20). However, SIBs showed a significant positive correlation between deep encoding task performance and cortical activity in the right IFG region [$r = .44$, $p < .05$]. Correlations in the other two ROIs were nonsignificant.

A potential confound with the current study concerned the gender composition of each group, as the SIB group had a larger proportion of males than did the SNC group (47.6% vs. 26.3%). In

Table 4. Levels-of-Processing Effects (Deep vs. Shallow Encoding)

| ROI	Brodmann Area(s)	X	Y	Z	ROI F Value for Main Effect of Depth	Effect Size
SCNs						
Left Inferior Frontal Gyrus	47	−52	27	−3	21.94	.7168
Left Cuneus	18	−22	−102	9	20.21	.7043
Left Superior Frontal Gyrus	6	−2	12	60	15.94	.4976
Right Cuneus	18	26	−99	9	10.52	.6347
Left Inferior Frontal Gyrus	46	−44	42	9	10.33	.5675
SIBs						
Left Middle Frontal Gyrus	6	−4	24	45	15.39	.7295
Left Inferior Frontal Gyrus	44	−46	12	27	14.48	.9717
Right Inferior Frontal Gyrus	47	40	24	0	9.08	.7629
Right Cerebellum		32	−69	−36	7.74	.8390
Left Inferior Frontal Gyrus	44/47	−40	39	0	7.65	.9512
Right Inferior Frontal Gyrus	44	44	42	0	7.15	.7936

ROI, region of interest; other abbreviations as in Table 1.
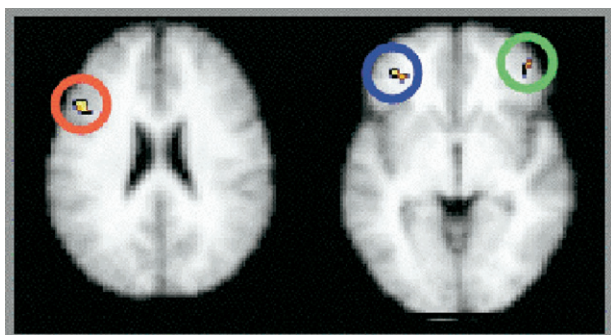
Figure 2. Regions which demonstrate a significant Group × Encoding Depth interaction: left IFG (BA 44; −44, 15, 27; circled in red), left IFG (BA 47; −32, 36, −3; circled in blue), and right IFG (BA 47; 40, 42, −3; circled in green). Siblings of individuals with schizophrenia demonstrated more activity during deep encoding in all three regions than control participants. (Note: Right side of image represents right side of brain, left side of image represents left side of brain.)

order to determine whether gender significantly affected the neuroimaging results, we performed repeated measures ANOVAs separately for each group in the three ROIs that showed significant between-group differences, similar to the procedure described above. Results of the ANOVAs indicated that the Group × Depth interaction remained significant independently for both males and females in all three ROIs.

Discussion

In this study, we aimed to determine whether the siblings of individuals with schizophrenia would show memory benefits after a levels-of-processing manipulation (i.e., deep encoding) and activate semantic processing regions typically activated in healthy individuals during deep encoding. We also predicted that the siblings of individuals with schizophrenia would show a pattern of enhanced bilateral PFC activity during deep encoding similar to that previously observed in schizophrenia subjects (Bonner-Jackson *et al.* 2005). Our predictions were confirmed in all three cases. Siblings of schizophrenia subjects, like healthy subjects, recognized significantly more deeply encoded words than shallowly encoded words, and activated brain regions commonly associated with semantic processing, including the left IFG (BA 44). However, siblings of schizophrenia subjects also activated regions in bilateral PFC during the deep verbal encoding task, including three regions of PFC not typically activated by healthy subjects.

We were somewhat surprised that SIBs showed similar levels of cognitive performance compared with healthy subjects after a levels-of-processing manipulation. Such a finding—unimpaired verbal memory performance in SIBs—has not been common in previous studies. Although some investigators have reported no significant differences in similar tasks between relatives of schizophrenia subjects and healthy subjects (Goldberg *et al.* 1990; Stratta *et al.* 1997), the majority of findings indicate some form of verbal memory impairment in the former group (Cannon *et al.* 1994; Hoff *et al.* 2005; Schubert and McNeil 2005; Sitskoorn *et al.* 2004; Sponheim *et al.* 2004; Toulopoulou *et al.* 2003a, 2003b). In light of our findings, it is possible that the verbal memory deficits seen in previous studies of relatives of schizophrenia subjects were the result of ineffective encoding strategies on their part, as has been previously suggested (Lyons *et al.* 1995). Consistent with this notion, there were episodic memory deficits (or trend-level differences) in the SIBs during neuropsy-

chological tasks for which there was no encoding support (e.g., Family Pictures, Logical Memory), similar to the pattern of memory deficits that has been demonstrated in schizophrenia (Brebion *et al.* 1997; Larsen and Fromholt 1976; Traupmann 1980). The performance differences between the in-scanner memory task, which relied on recognition, and the neuropsychological tasks administered outside of the scanner, which were recall measures, might stem from differential discriminability of the two task types. Traditionally, memory tasks that require recall are more cognitively demanding and rely on conscious recollection on the part of the participant. In contrast, recognition of items can be accomplished on the basis of familiarity, as opposed to recollection, and could potentially artificially equate the performance of the two groups in our study. Thus, our results suggest that deficits in generating effective strategies for verbal encoding might be, at least in part, indicative of genetic liability for schizophrenia. Further work will be needed to confirm this hypothesis.

Previous work in healthy populations has identified several regions of PFC, including left IFG (BA 45/47), in which encoding-related activity reliably predicts subsequent retrieval success (Buckner *et al.* 2001; Fletcher *et al.* 2003; Kapur *et al.* 1994; Wagner *et al.* 1998). Our results indicate that SIBs, like individuals with schizophrenia, activate these regions when engaged in the deep verbal encoding task. However, in addition to showing brain activity in a number of the regions activated by control participants, SIBs also showed significantly more cortical activity than control subjects in three subregions of PFC during deep verbal encoding—two areas of left IFG (BA 44 & 47) and one area of right IFG (BA 47). These results are strikingly similar to the pattern of brain activity we found previously during deep semantic encoding in individuals with schizophrenia (Bonner-Jackson *et al.* 2005) and are in line with previous findings of overactivity in PFC during memory task performance in relatives of individuals with schizophrenia (Callicott *et al.* 2003; Thermenos *et al.* 2004; Whyte *et al.* in press). Moreover, this increased deep encoding-related activity in bilateral PFC was primarily seen in schizophrenia subjects who performed poorly, which suggests that the increased activity seen in frontal cortex is pathological.

Contrary to this hypothesis, however, high-performing siblings in this study (M = .87) showed larger encoding-related differences in activity than lower-performing siblings (M = .75). Furthermore, correlations between encoding task performance and cortical activity in the three regions showing between-group differences demonstrated that activity in right IFG (BA 47) was significantly positively correlated with deep encoding task performance in SIBs. Our results suggest that the additional activity seen in bilateral PFC in SIBs might represent a compensatory mechanism associated with better task performance, although the reduced amount of variance in the encoding performance data renders any conclusions preliminary at best, and nonsignificant results should be interpreted cautiously. Indeed, cortical activity in the two left IFG regions activated by SIBs (BA 44 & 47) has previously been associated with successful encoding and semantic processing in healthy control participants (McDermott *et al.* 2003; Otten *et al.* 2001). As such, greater activation of this region in SIBs might reflect either greater effort devoted to semantic processing or less efficient activation of this region. The role that the homologous right BA 45/47 plays is less clear. There is some indication from the lesion literature that activity in right PFC regions might be compensatory in the event of left-lateralized PFC damage (Blasi *et al.* 2002). It is intriguing to speculate that genetic predisposition to schizophrenia might cause left PFC dysfunction, thereby necessitating the recruitment of right

PFC to accomplish cognitive tasks involving semantic processing or other aspects of language processing.

In summary, the results of the current study indicate that SIBs show significantly better recognition for deeply encoded rather than shallowly encoded words and activate typical semantic processing regions while engaging in deep verbal encoding. Additionally, SIBs, like their ill relatives, activated a wider set of PFC brain regions during deep verbal encoding not typically activated by healthy subjects. Taken together, our results suggest that alterations in task-related functional brain activation during verbal memory encoding represent a potential endophenotype marker of genetic liability for schizophrenia. Future work in this area should examine the degree to which severity of episodic memory deficits and associated functional brain activation disturbances predict the subsequent development of psychotic symptoms. It will also be important to investigate the relationship between functional brain activity deficits and abnormalities of brain structure, both in individuals with schizophrenia and their first-degree relatives.

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