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Neuropsychologia 43 (2005) 930–942

NEUROPSYCHOLOGIA

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Working memory functioning in schizophrenia patients and their first-degree relatives: cognitive functioning shedding light on etiology☆

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Received 10 September 2003; received in revised form 18 June 2004; accepted 1 September 2004

Abstract

There is accumulating evidence for involvement of the prefrontal cortex (PFC) in the pathophysiology of schizophrenia. A primary function supported by the PFC is working memory (WM). Findings from WM studies in schizophrenia can provide insight into the nature of clinical symptoms and cognitive deficits associated with this disorder, as well as begin to suggest areas of underlying neuropathology. To date, studies have not adequately investigated different WM domains (e.g., verbal, spatial, or object) or processing requirements (e.g., maintenance, monitoring, or manipulation), shown to be associated with distinct patterns of neural activation, in schizophrenia patients and their well relatives. Accordingly, this study evaluated the performance of schizophrenia patients, their first-degree biological relatives, and nonpsychiatric controls on a comprehensive battery of WM tasks and investigated the association among WM deficits and schizophrenia-spectrum psychopathology. The findings indicate that schizophrenia patients are consistently impaired on WM tasks, irrespective of WM domain or processing requirements. In contrast, their unaffected relatives are only impaired on WM tasks with higher central executive processing requirements. This pattern of WM performance may further implicate DLPFC dysfunction in the liability for schizophrenia and has implications for future cognitive, genetic, and neurodevelopmental research.

Keywords: Dorsolateral prefrontal cortex (DLPFC); Endophenotype; Domain-specific; Process-specific; Central executive; Schizotypy

Schizophrenia is a debilitating disorder for which, despite decades of research, there has been no discovery of a specific causal factor. Research has provided accumulating evidence for involvement of the prefrontal cortex (PFC) in disorder pathophysiology. For over half a century, it has been appreciated that a constellation of symptoms central to the schizophrenia diagnosis (negative symptoms) resembles the behavior of individuals with frontal lobe dysfunction (Bleuler, 1950; Kraepelin, 1971). For example, avolition, apathy, inappropriate or flat affect, social withdrawal, and impaired judgment characterize both schizophrenia and frontal lobe dysfunction secondary to brain injury or disease (Stuss & Benson, 1984). Subsequently, neurocognitive investigations of schizophrenia patients have revealed impairment on tasks sensitive to frontal lobe lesions including continuous performance tasks (e.g., Laurent et al., 1999; Nuechterlein, Dawson, & Green, 1994), delayed response tasks (DRT) (e.g., Park & Holzman, 1992; Snitz, Curtis, Zald, Katsanis, & Iacono, 1999), delayed alternation tasks (e.g., Seidman et al., 1995), and the Tower of London (e.g., Morice & Delahunty, 1996). Convergent evidence for compromised PFC functioning in schizophrenia also comes from neurophysiological studies demonstrating smooth pursuit eye movement dysfunction (e.g., Iacono, 1998), and increased rates of reflexive errors on antisaccade tasks (e.g., Curtis, Calkins, Grove, Feil, & Iacono, 2001).

☆ Portions of this paper were presented at the Society of Biological Psychiatry in Chicago, Illinois, May 11–13, 2000.

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0028-3932/$ – see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.neuropsychologia.2004.09.013

Inferences based on clinical phenomenology, neurocognitive performance, and neurophysiological functioning have been substantiated by more direct measures of neuroanatomy, including findings from neuroimaging and post-mortem histological studies. For example, some structural neuroimaging studies (e.g., Andreasen et al., 1986; Breier et al., 1992; Raine et al., 1992; but see Andreasen et al., 1990; Kelsoe, Cadet, Pickar, & Weinberger, 1988 for contrary results) have found evidence for reduced PF cortical volume in schizophrenia patients when compared to healthy and psychiatric control subjects. Further, several functional neuroimaging studies have reported evidence for reduced frontal lobe activation (hypofrontality) in schizophrenia patients, especially during performance of putative frontal lobe tasks (e.g., Callicott et al., 1998; Weinberger, Berman, & Zec, 1986; Yurgelun-Todd et al., 1996). Findings from neuroimaging studies have been supported at the cellular level. Post-mortem histological studies indicate neuronal loss and disturbances in neuronal distribution in the frontal and temporal lobes (e.g., Benes, 1995; Bogerts, 1993).

A primary function supported by the frontal lobes is working memory (WM). WM has been defined as a system used for the temporary maintenance and manipulation of information required for the performance of many complex tasks (Baddeley, 1998a). Baddeley and Hitch proposed a tripartite WM model composed of an attentional control system, the central executive, and two slave systems, the phonological loop and the visuospatial sketch pad (Baddeley, 1998b). Although Baddeley was hesitant to make specific predictions about the neural substrates underlying component processes of WM, findings from neuroimaging studies have been remarkably consistent with their model. For example, studies have reliably identified distinct patterns of neural activation associated with the type of information held in WM (e.g., verbal or spatial), as well as the type of processing performed upon such information (e.g., simple storage or rehearsal). For a review, see Smith and Jonides (1998).

Opinions diverge when it comes to identifying the neural substrates supporting central executive processes of WM. While most researchers agree that executive processes are mediated by the PFC, two competing theories ascribe different functions to distinct areas within the PFC, the dorsolateral PFC (DLPFC) and ventrolateral PFC (VLPFC). The *domain-specific model* posits that the lateral PFC is organized according to type of information held in WM, with spatial information mediated by the DLPFC and nonspatial information mediated by the VLPFC (Goldman-Rakic, 1995). The *process-specific model* posits that the lateral PFC is organized according to type of processing performed upon information in WM, with DLPFC only activated by tasks that require active manipulation or monitoring of information, in addition to maintenance in WM (Petrides, 1995).

Evolution of the WM construct and mapping of neural substrates subserving WM processing are instrumental not only in elucidating how the healthy human brain functions but also in unraveling processes underlying mental disorders as complex as schizophrenia. Findings from WM studies in schizophrenia can provide insight into clinical symptoms and cognitive deficits associated with this disorder, as well as suggest areas of underlying neuropathology. The continued discovery of neuropathological sites is instrumental to fleshing out the etiological picture of schizophrenia, as well as eventually suggesting rational treatment approaches.

Studies investigating WM performance of schizophrenia patients reveal impairment that cuts across WM domains, with patients performing significantly worse than healthy controls on verbal (e.g., Carter et al., 1998; Conklin, Curtis, Katsanis, & Iacono, 2000; Gold, Carpenter, Randolph, Goldberg, & Weinberger, 1997), spatial (e.g., Pantelis et al., 1997; Park & Holzman, 1992; Snitz et al., 1999), and object (e.g., Glahn, Cannon, Gur, Ragland, & Gur, 2000; Hutton et al., 1998; Spindler, Sullivan, Menon, Lim, & Pfefferbaum, 1997) WM tasks. Findings of cognitive deficits in schizophrenia, including WM, are sometimes difficult to interpret because factors associated with mental illness (e.g., active psychotic symptoms, lower education levels, or medication effects) could potentially influence task performance and are difficult to disentangle from effects of basic neuropathology. Provided that cognitive deficits reflect the underlying risk for schizophrenia, it is beneficial to study first-degree biological relatives of schizophrenia patients because they share, on average, some of the genetic diathesis for this disorder without presenting the same experimental difficulties. While relatives demonstrate less consistent WM impairment than schizophrenia patients, both groups exhibit WM deficits in multiple domains (i.e., verbal: Conklin et al., 2000; and spatial: Park, Holzman, & Goldman-Rakic, 1995).

There continue to be unanswered questions pertaining to WM functioning in schizophrenia that warrant experimental investigation. To date, no identified studies have examined more than a couple WM measures within the same group of schizophrenia patients (e.g., Coleman et al., 2002; Spindler et al., 1997) or relatives, necessitating comparison of measures across research samples that may differ in ways that contribute to WM findings (e.g., the composition of the schizophrenia group). The extant literature examining WM functioning in relatives is especially limited, with a paucity of studies investigating certain WM domains and processing demands. For example, no study, of which we are aware, has examined the performance of relatives on measures of object WM, on verbal WM measures with higher processing demands than Digit Span Tasks, or on measures requiring substantial monitoring of information within WM (i.e., self-ordered or *n*-back tasks). Finally, studies have failed to fully investigate the relationship among WM impairment and schizophrenia or schizophrenia-spectrum symptomatology (e.g., positive and negative symptoms in schizophrenia patients or schizotypy in relatives).

The primary objective of the current study is to evaluate the performance of schizophrenia patients, their first-degree biological relatives, and nonpsychiatric controls on a battery of WM measures that vary in information do-

main and processing requirements. Provided group differences are revealed, the relationship among WM deficits and schizophrenia-related symptomatology will be investigated. We predict that schizophrenia patients will be impaired on the majority of WM measures and performance will be inversely associated with the presence of negative symptoms, as both are putative indicators of frontal lobe functioning. In contrast, we hypothesize that nonpsychotic relatives of schizophrenia patients will only be impaired on a subset of WM measures, those measures that require greater executive processing (e.g., reshuffling of information or protection from interference), irrespective of WM domain. On such tasks, we predict that the performance of relatives will be intermediate to patients and controls, as only a subset of relatives likely has the underlying diathesis for schizophrenia. The investigation of relationships among WM performance and schizotypy in the relative group is largely exploratory in nature given that the research literature does not provide enough evidence to warrant specific predictions. However, if these neuropsychological and personality measures are tapping the same schizophrenia diathesis, relatives higher in schizotypal traits should also demonstrate greater WM impairment.

1. Method

1.1. Participants

The participants in this study represent a subset of individuals who took part in the Research in Schizophrenia (RISC) Project, a study investigating psychophysiological, neuropsychological, and behavioral indices of risk for schizophrenia. The Internal Review Boards of the University of Minnesota and Regions Hospital approved this protocol in 1995 and annual re-approval was ascertained until study termination. Some methods used in participant selection, diagnostic assignment, and general cognitive assessment have been described previously (Conklin, Calkins, Anderson, Dinzeo, & Iacono, 2002). All participants provided written informed consent prior to study inclusion and were compensated for study participation.

Schizophrenia patients were recruited from acute-care units of a regional metropolitan hospital. All patients met Diagnostic and Statistical Manual for Mental Disorders-Fourth Edition (DSM-IV; American Psychiatric Association [APA], 1994) criteria for schizophrenia, based on diagnostic interviewing using the Structured Clinical Interview for DSM-IV (SCID-IV; First, Spitzer, Gibbon, & Williams, 1995) and medical record review. None of the patients had a history of neurological disease, systemic disease with known CNS sequelae, clinically significant head injury, or recent ECT treatment. All patients were between the ages of 18 and 65, spoke English fluently, were literate, and were never diagnosed with mental retardation. Patients had a negative urine toxicology screen upon hospital admission or a minimum of 14 days inpatient stay between positive urine toxicology screen date and testing. Hospital records containing medication information were obtained in order to determine specific drug names and dosages.

Normal control participants were recruited from the community via advertisement posters placed at regional hospital clinics and community vocational/technical schools, as well as through announcements at local churches. Control participants were excluded for the same general and medical criteria as the patients, as determined by health history interview. They were additionally excluded if they had any lifetime diagnoses of major affective, psychotic, or substance dependence disorder, as determined by the SCID-IV, and if they or a first-degree biological relative had ever sought mental health treatment.

First-degree biological relatives from 18 families of the schizophrenia patients were recruited through written correspondence followed by phone contact. Relatives were excluded for the same general and medical criteria as the schizophrenia patients. They were also interviewed using the SCID-IV. Analyses were conducted both with a subgroup of relatives who met the rigorous diagnostic inclusion criteria established for the normal control participants and with a larger group that only excluded individuals with lifetime diagnoses of a psychotic disorder, current mood disorder, or current substance use disorder (i.e., includes relatives who meet lifetime, but not current, diagnoses of major affective or substance dependence disorder).

1.2. Procedure

1.2.1. Assessment of psychopathology

All participants were interviewed using the SCID-IV (Modules A–E). In order to confirm diagnostic assignment, the SCID-IV, chart data and, when necessary, audio recordings of interviews, were reviewed by a consensus team composed of clinical psychologists and advanced doctoral level students. A high level of diagnostic agreement was established by a reliability study performed on a group of 50 patients with diagnoses of schizophrenia, schizoaffective, and psychotic mood disorders ($\kappa = 0.84$).

A subset of schizophrenia patients ($n = 34$) was interviewed using the Positive and Negative Syndrome Assessment Scale (PANSS; Kay, Fiszbein, & Opler, 1987), a measure added after the study had begun. These questions, which evaluate the presence of psychopathology in the preceding month, were asked during diagnostic interviewing with the SCID-IV. The PANSS consists of 30 items that are rated on a seven-point scale, from symptom not present at all to symptom present to an extreme degree. The questions comprise three scales: negative symptoms (7 items), positive symptoms (7 items), and general psychopathology (16 items).

Control participants and relatives were administered the Schizotypal Personality Questionnaire (SPQ; Raine, 1991), which is a self-report measure based on DSM-III-R (APA, 1987) criteria for schizotypal personality disorder (SPD). The SPQ assesses the nine major criterial features of SPD

in DSM-IIIR that contribute to three factors, as revealed by confirmatory factor analysis: cognitive-perceptual, social-interpersonal, and disorganization (Raine et al., 1994). The SPQ was modified to include 15 items from the L (lie) Scale and 30 items from the K (defensiveness) Scale of the Minnesota Multiphasic Personality Interview-Second Edition (MMPI-2; Butcher, Dahlstron, Graham, Tellegen, & Kaemmer, 1989), in order to assess under-reporting of symptoms and response bias. Seven items from the Jackson Infrequency Scale were used to detect random responding (Jackson, 1984). These items were interspersed among the 74 SPQ items to form a 126 item True/False instrument. Participants were asked to refrain from considering times when they were under the influence of drugs or alcohol and periods when they were just falling asleep or awakening when responding to items.

1.2.2. Assessment of working memory

In order to assess verbal WM, all participants were administered the Wechsler Digit Span Task (Wechsler, 1981) and Letter-Number Sequencing Task (Wechsler, 1997). The Digit Span Task is composed of Digit Span Forward and Digit Span Backward. In both subtasks, the examiner verbally presents specified sequences of random digits at a rate of one per second. Digit Span Forward requires the participant to repeat back the digits verbatim. Digit Span Backward requires the participant to repeat back the digits in reverse order. The number of digits increases by one until the participant consecutively fails two trials of the same length. In the Letter-Number Sequencing Task, the examiner verbally presents specified sequences of random digits and letters at a rate of one per second. The participant is required to repeat back the numbers first, in order from smallest to largest, followed by the letters, in alphabetical order. The number of digits and letters increase by one until the participant consecutively fails three trials of the same length.

To assess spatial WM, all participants were administered the Wechsler Spatial Span Task (Wechsler, 1997) and a computerized visual-manual delayed response task adapted from Luciana, Depue, Arbisi, and Leon (1992). The Spatial Span Task, created to be a visual analogue of the Digit Span Task, is composed of Spatial Span Forward and Spatial Span Backward. Both subtasks use a Spatial Span Board that consists of 10 blue cubes fastened to a white plastic board. The examiner taps specified sequences of blocks of random location at a rate of one per second. Spatial Span Forward requires the participant to repeat the block taps in the same order. Spatial Span Backward requires the participant to repeat the block taps in reverse order. The number of blocks increases by one until the participant fails two trials of the same length.

For the DRT task, participants were seated in a quiet darkened room, with their heads stabilized by a chin and headrest, and their eyes 27 cm from the computer monitor. Four different DRT conditions were employed: a no-delay control, a 0.5 and 8 s delay without interference, and an 8 s delay with interference. Trials began with the participant fixating on a small cross in the center of the screen. After 2 s, a target stimulus (asterisk) appeared at one of 16 positions evenly distributed along an imaginary circle 4.5 cm from the fixation point. For each trial, the participant was required to indicate the location of the target stimulus by touching the screen with a light-pen. For the no-delay condition, the target remained on the screen while the subject responded; this condition served as a sensory-motor control. For the delay without distraction conditions, the target appeared for 200 ms, the screen turned dark for the delay (0.5 or 8 s), and then the screen lightened cueing a response. Thirty-two trials were presented, with all 16 target positions paired with either a 0.5 or 8 s delay, and trials intermixed by delay interval. The 8 s delay with interference condition included 16 trials where the participant read three or four letter words, one word per every 2 s, throughout the delay period. For each trial, the distance between target location and subject response was calculated and transformed into an error score in mm. Approximately halfway through this study, the DRT was altered to include a fixation cross that remained on during the delay period of non-distraction conditions and feedback in the form of the target stimuli reappearing after each subject response. These changes were implemented to increase standardization of participant behavior during the delay period (i.e., looking at the fixation point) and to maximize motivation by providing feedback about accuracy.

Object WM was assessed by a computerized self-ordered pointing task (SOP) modeled after Petrides and Milner (1982). Again, participants were seated in a quiet darkened room, with their heads stabilized by a chin and headrest, and their eyes 27 cm from the computer monitor. Eleven geometric line drawings of objects were presented in an imaginary 3×4 matrix. Participants were instructed to use the light-pen to choose each object once, and only once, in any order. After the participant's response, the objects were randomly rearranged in the matrix, cueing initiation of the next response. The task ended when all objects had been selected or 30 trials had been presented, whichever occurred first. During the task, the location of the most recently selected object was muted with a black square that did not accept a response for the subsequent trial. This procedure precluded responding to the same location and capitalizing on the randomization of object presentation (Curtis, Zald, & Pardo, 2000). Both the random rearrangement of objects and muting of previous responses limited spatial mnemonic strategies. Objects were selected that are not readily namable in order to limit the use of verbal mediation.

1.2.3. Assessment of general cognitive ability

To obtain an estimate of general cognitive functioning, all participants were administered the WAIS-R Block Design subtest, which requires the examinee to replicate models or pictures of designs with blocks, and the WAIS-R Information subtest, which requires the examinee to respond orally to a series of questions assessing general knowledge (Wechsler, 1981). IQ was prorated using scores on the Block Design and

Information subtests according to the procedure developed by Tellegen and Briggs (cited in Sattler, 1990). Four patients, but no relatives or controls, were excluded for having an IQ < 70, a defining feature of mental retardation.

1.3. Data analytic plan

Group differences in WM performance were investigated with mulivariate statistics carried out for each WM measure individually. Appropriate statistics were used to evaluate group differences in demographic variables and associations among demographic variables with WM perfromance. Given that groups differed significantly on demographic variables, analyses of covariance (ANCOVAs) with age, education, and IQ, entered separately, as covariates were conducted. Since relatives were selected for their genetic relationship to schizophrenia probands and some relatives came from the same families, some observations included in statistical analyses were not independent. In order to correct for violating the statistical assumption of independence, the degrees of freedom used to derive *p* values in all *t*-tests, ANOVAs, ANCOVAs, and post hoc comparisons were adjusted by replacing the number of individuals with the number of families. Adjusted *p*-values are presented in the text. For exploratory analyses, Bonferonni Corrections, using significance values derived by dividing *p* by the number of statistical comparisons, were used to account for multiple comparisons.

2. Results

2.1. Exploratory procedures

Within group *t*-tests comparing the no-fixation and fixation mean error scores for each DRT condition (0 s delay, 0.5 s delay, 8 s delay, and 8 s interference) failed to reveal significant differences between task versions, suggesting that changes to the task did not systematically affect participant performance. Therefore, the within group-within condition means and standard deviations of both task versions were used to convert scores from the no-fixation version to scores producing the same mean and standard deviation as the fixation version.[1] Following this data transformation procedure, data from the two tasks were combined. Subsequent discussions of the DRT (including tabular and graphic presentations) reflect this transformed dataset.

[1] Data were transformed using the formula $x'_1 = (x_1 - \mu_1)/\sigma_1\sigma_2 + \mu_2$, where x'_1 is the transformed score, x_1 is the score on the no-fixation task version, μ_1 is the mean of the no-fixation task version for a particular group and condition, σ_1 is the standard deviation of the no-fixation task version for a particular group and condition, σ_2 is the standard deviation of the fixation task version for a particular group and condition, and μ_2 is the mean of the fixation task version for a particular group and condition.

2.2. Demographics

Table 1 presents the means, standard deviations, and test statistics for relevant demographic and neuropsychological variables. The groups did not differ significantly in gender composition. *t*-tests comparing the performance of males and females, within each group separately, were computed for all dependent variables from the WM tasks. None of these *t*-tests revealed significant gender differences. In addition, gender was not found to correlate with performance on any of the WM tasks, in any of the groups. Given that gender ratios did not differ among groups and gender was not related to performance on WM tasks, gender was not considered as a factor in the remaining analyses. Groups differed significantly in age. Relatives were significantly older than controls and patients, who did not differ from each other. Education level differed significantly among groups. Controls had more years of education than relatives and patients, who did not differ from each other. There was a significant difference among groups in IQ. Controls had a higher IQ than relatives who had a higher IQ than patients.

2.3. Working memory performance by separate domains

2.3.1. Verbal working memory

There was a significant difference among groups on Digit Span Forwards and Digit Span Backwards. On Digit Span Backwards schizophrenia patients recalled fewer digits than relatives who recalled fewer digits than controls. On Digit Span Forwards schizophrenia patients and relatives recalled fewer digits than controls, but did not differ significantly from each other. Impaired Backward Digit Span performance in relatives is a replication of previous findings with an independent sample (Conklin et al., 2000). Groups differed significantly on Letter-Number Sequencing. Schizophrenia patients recalled fewer items than relatives who recalled fewer items than controls.

2.3.2. Spatial working memory

There was a significant difference among groups on Spatial Span Forwards and Spatial Span Backwards. Schizophrenia patients recalled fewer items than relatives and controls on both tasks. Relatives and controls did not differ on either task. A repeated-measures ANOVA, with condition (0 s delay, 0.5 s delay, 8 s delay, and 8 s interference) as the within subject factor and group (schizophrenia, relative, and control) as the between subject factor was conducted. There was a significant interaction between DRT performance and group membership ($F = 8.31$, d.f. = 6, 278, $p < 0.001$). There was also a significant main effect for DRT condition ($F = 544.16$, d.f. = 3, 138, $p < .001$), indicating poorer performance was associated with longer delay, and a main effect for group ($F = 22.70$, d.f. = 2, $p < 0.001$), suggesting that the schizophrenia group performed worse than the other two groups. There were no significant group differences during the 0 s control condition nor the 0.5 s delay. For the 8 s delay and 8 s interference

Table 1
Demographic, neuropsychological, and clinical information by group

Variable	Schizophrenia ($N = 39$[a])	Relative ($N = 33$[a])	Control ($N = 56$[a])	Test statistic	Probability	Post hoc tests (LSD)			Effect size		
						S v. C	R v. C	R v. S	S v. C	R v. C	R v. S
Demographics											
Gender ratio (% male)	60.0	51.5	41.1	$\chi^2(2) = 3.04$	0.22	–	–	–	–	–	–
Age (years)	37.8 ± 8.2	43.9 ± 10.8	33.6 ± 12.9	$F(2,125) = 8.97$	<0.001	0.08	<0.01*	0.02*	0.37	0.85*	0.65*
Education (years)	13.1 ± 1.8	13.9 ± 2.0	15.9 ± 2.5	$F(2,125) = 20.59$	<0.001	<0.01*	<0.01*	0.15	−1.24*	−0.87*	0.40
Prorated IQ	93.8 ± 13.4	102.8 ± 12.5	111.6 ± 15.4	$F(2,125) = 18.40$	<0.001	<0.01*	0.01*	0.01*	−1.22*	−0.61*	0.67*
Neuropsychological test scores											
Digit Span Forward[b] (Wechsler Raw Score)	7.0 ± 2.4	8.0 ± 2.2	9.0 ± 2.4	$F(2,134) = 9.18$	<0.001	<0.01*	0.04*	0.06	−0.83*	−0.43*	0.43
Digit Span Backward[b] (Wechsler Raw Score)	5.6 ± 2.5	6.9 ± 2.1	8.2 ± 2.5	$F(2,134) = 14.44$	<0.001	<0.01*	0.01*	0.02*	−1.04*	−0.56*	0.55*
Letter-Number Sequencing (Wechsler Raw Score)	7.8 ± 2.8	10.4 ± 2.2	12.2 ± 2.9	$F(2,125) = 30.44$	<0.001	<0.01*	<0.01*	<0.01*	−1.55*	−0.66*	1.03*
Spatial Span Forward (Wechsler Raw Score)	8.0 ± 1.8	9.2 ± 1.8	9.3 ± 1.6	$F(2,125) = 7.05$	<0.001	<0.01*	0.86	<0.01*	−0.77*	−0.06	0.67*
Spatial Span Backward (Wechsler Raw Score)	7.1 ± 2.4	8.0 ± 1.4	8.6 ± 1.3	$F(2,125) = 8.62$	<0.001	<0.01*	0.16	0.02*	−0.82*	−0.40	0.48*
DRT[c] 0 s delay (distance from target (mm))	2.4 ± 1.0	2.0 ± 0.9	2.0 ± 0.7	$F(2,140) = 2.54$	0.08	NS	NS	NS	0.48	0.00	−0.42
DRT 0.5 s delay (distance from target (mm))	6.8 ± 1.5	6.4 ± 2.1	6.3 ± 1.4	$F(2,140) = 1.33$	0.27	NS	NS	NS	0.35	0.06	−0.22
DRT 8 s delay (distance from target (mm))	11.9 ± 3.5	9.4 ± 2.8	9.3 ± 2.1	$F(2,140) = 13.50$	<0.001	0.00	0.83	<0.01*	0.96*	0.05	−0.80*
DRT 8 s interference (distance from target (mm))	16.2 ± 4.5	11.6 ± 5.1	10.6 ± 3.0	$F(2,140) = 24.45$	<0.001	<0.01*	0.25	<0.01*	1.52*	0.24	−0.96*
Self-ordered pointing[d] (number of trials to completion)	21.5 ± 6.4	20.5 ± 6.5	16.6 ± 4.6	$F(2,124) = 9.66$	<0.001	<0.01*	<0.01*	0.45	0.91*	0.72*	−0.16

Note. Data are presented as means plus or minus the standard deviation, unless otherwise indicated. S v. C: a comparison of schizophrenia patients and controls. R v. C: a comparison of relatives and controls. R v. S: a comparison of relatives and schizophrenia patients. Effect sizes (d) were calculated using the sample-size weighted pooled within-group standard deviation to provide estimates of group differences independent of sample size (Hunter & Schmidt, 1990). DRT: delayed response task. The degrees of freedom used to derive p values in all t-tests, ANOVAs, ANCOVAs, and post hoc comparisons were adjusted by replacing the number of individuals with the number of families. When this conservative statistical procedure was used, all significant analyses remained significant ($p < 0.05$). ANCOVAs with age, education, and IQ, entered separately, as covariates were conducted. All previously reported differences on WM tasks between patients and controls remained significant except on Spatial Span Backwards when adjusting for IQ ($p = 0.25$). All previously reported differences between relatives and controls remained significant except for the difference on Digit Span Backwards was reduced to a trend after adjusting for education or IQ ($p = 0.13$ and 0.09) and the difference on Letter-Number Sequencing was reduced to a trend after adjusting for IQ ($p = 0.07$). Given the moderate-to-high correlation between IQ and WM (e.g., Wechsler, 1997), it is likely that meaningful variance is being removed from the comparison of groups on WM tasks when entering IQ as a covariate, thus reducing the interpretability of these secondary findings.

[a] Sample size unless otherwise noted.

[b] The Digit Span Backward Task (patient $N = 42$, relative $N = 37$ and control $N = 58$).

[c] The DRT (patient $N = 43$, relative $N = 40$ and control $N = 60$) were added to the neuropsychological battery before Spatial Span, Letter-Number Sequencing, and the self-ordered pointing tasks, thus providing data for additional subjects.

[d] One patient was discharged prior to completing testing reducing the number of patient subjects for the self-ordered pointing task to 38.

* Indicates a significant difference between groups as determined by LSD post hoc tests, $p < 0.05$.

conditions, group differences reached significance. Schizophrenia patients had a larger error score than relatives and controls, who did not differ from each other.

2.3.3. Object working memory

There was a significant difference among groups on the SOP task. Controls required significantly fewer trials to solve the task than schizophrenia patients and relatives, who did not differ significantly from each other. Further examination of the data indicated that 20% of patients and relatives ($N = 8$ and $N = 7$, respectively), compared to 2% of controls ($N = 1$), failed to reach solution prior to task termination (= 30 trials). These differences in the proportion of individuals reaching solution were statistically significant ($X^2 = 9.71$, d.f. = 1, $p = 0.002$ and $X^2 = 9.58$, d.f. = 1, $p = 0.002$ for patients and relatives, respectively).

2.4. Working memory performance and psychopathology

Performance of schizophrenia patients on the PANSS and SCID were used to quantify symptom severity (PANSS, general scale = 31.9 ± 7.0, positive scale = 20.9 ± 5.8 and negative scale = 14.0 ± 4.4; GAF 27.7 ± 11.7). In order to investigate the relationship among WM performance and schizophrenia symptomatology, correlations among the WM tasks and the PANSS scales were examined. Contrary to our predictions, within the schizophrenia group, none of the WM tasks correlated significantly with the negative PANSS scale ($-0.08 < r$'s < 0.26, $0.17 < p$'s < 0.66). None of the WM tasks correlated significantly with the positive PANSS scale either ($-0.16 < r$'s < 0.30, $0.10 < p$'s < 0.88). The only correlation to reach significance was between the general PANSS scale and the 8 s delay condition on the DRT ($r = 0.34$, $p = 0.05$). This correlation is not statistically significant after using the Bonferonni Correction for multiple comparisons, suggesting that it may be spurious.

It has previously been shown using a larger sample, partially overlapping with this one, that there is a significant difference between relatives and control participants in schizotypal symptoms as measured by the SPQ (Calkins, Curtis, Grove, & Iacono, 2004). Individual *t*-tests between relatives and controls failed to reveal significant differences on any of the validity scales (i.e., MMPI-2 L and K scales, Jackson Infrequency Scale). Given that the groups did not differ in measured response biases or random responding, all available SPQ scores were considered (one control's data was excluded because the individual responded both true and false to multiple items). There was only one significant correlation among the dependent variables from the WM tasks and the SPQ total and factor scores, performance on Letter-Number Sequencing and Factor 3 (disorganization; $r = 0.45$, $p = 0.01$). This correlation is not in the predicted direction (i.e., greater disorganization was associated with a longer Letter-Number Span) and did not remain significant after a Bonferonni Correction, reducing the likelihood that this correlation indexes a meaningful relationship. There were no significant correlations among WM tasks and the SPQ total and factor scores within the control group.

Given that Factor 2 (social-interpersonal) was the factor that best differentiated groups in the previous study (Calkins et al., 2004), and is most similar to negative symptoms in schizophrenia patients, the relative group was subsequently divided into high and low Factor 2 scorers (a score greater than one standard deviation above the control mean and within one standard deviation of the control mean, respectively) and performance on WM tasks was compared. These *t*-tests revealed that relatives endorsing the greatest number of social-interpersonal schizotypal traits performed significantly worse on the SOP task than relatives endorsing traits at a level comparable to control participants ($t = 2.07$, $p = 0.048$). This difference is not significant when a Bonferonni Correction is used for multiple comparisons.

2.5. Working memory performance in the restricted relative group

The preceding analyses were conducted with a relative group meeting inclusion criteria that were less rigorous than criteria applied to the control group. Given the possibility that identified cognitive deficits could reflect the presence of psychopathology in the relative group, rather than genetic vulnerability for schizophrenia, all analyses were repeated with a relative group that met inclusion criteria established with control participants. The relatives omitted from these analyses all had a prior history of Major Depressive Disorder ($N = 3$) or Substance Dependence ($N = 3$). All statistically significant findings remained significant within this restricted relative group.

2.6. Working memory performance and psychotropic medications

There were no significant correlations among WM dependent variables and neuroleptic dose (in chlorpromazine equivalents). The performance of patients taking typical neuroleptic medication versus atypical neuroleptic medication was compared using *t*-tests for each dependent variable (after excluding individuals taking both typical and atypical neuroleptics). Two out of eight of these *t*-tests reached significance, with patients taking typical neuroleptics performing worse on the 0.5 and 8 s delay conditions of the DRT than patients taking atypical neuroleptics. Therefore, patients taking only typical neuroleptics ($N = 4$) were removed. Analyses investigating group differences on these two DRT conditions were repeated with the same results. *t*-tests between patients taking antiparkinsonian and patients not taking antiparkinsonian medication were computed for each dependent variable. None of these *t*-tests reached significance. Taken together,

these findings suggest that medication status is not significantly contributing to group differences on WM tasks.

2.7. Results following statistical adjustments

Conservative statistical approaches described in the data analytic plan (i.e., ANCOVAs to adjust for group differences in demographic variables and adjusting degrees of freedom to reflect number of families rather than individuals) had little effect on results; therefore, outcomes are described in the table note only, with footnoted reference to effects that changed as appropriate. As the probability column in Table 1 indicates, all of the significant test statistics generated $p < 0.001$.

3. Discussion

D'Esposito et al. (1998) plotted areas of lateral PFC activation on a standardized brain for all neuroimaging studies investigating WM performance in healthy controls that provided Talairach coordinates ($N = 20$). These plots failed to show a dorsal/ventral dissociation based on WM domain, with spatial and nonspatial activations distributed throughout the PFC. In contrast, when tasks were divided into "maintenance-only" and "maintenance-plus" tasks, there was a dorsal/ventral dissociation with maintenance-plus studies activating more dorsal substrates. Maintenance-only tasks were defined as tasks that require active maintenance of information across a nondistracted delay period. Maintenance-plus tasks were defined as tasks requiring reshuffling of, or processing of intervening stimuli during, the maintenance of information in working memory. Standard delayed response tasks without interference trials were provided as examples of maintenance-only tasks, whereas, self-ordered tasks and *n*-back tasks were provided as examples of maintenance-plus tasks. The study conducted by D'Esposito et al. (1998) may provide a useful cognitive heuristic for considering results in the current study.

Fig. 1 displays group performance on all WM tasks as *z*-scores, with the control group mean set to zero. As predicted, schizophrenia patients consistently demonstrated impaired performance on WM tasks, irrespective of WM domain or processing requirements. Their level of performance was at least one standard deviation below control participants on all tasks and significantly worse than their well relatives for all but one task (SOP). The pattern of deficits in these patients partially mirrored that found in their relatives, with the biggest deviation between patients and relatives on the DRT 8 s interference condition. Previous research has demonstrated that patients exhibit a disproportionate decline in performance, compared to controls or their relatives, with the addition of interference to WM tasks (e.g., Bowen et al., 1994; Corrigan & Green, 1991; Docherty & Gordinier, 1999). This finding may be indicative of attention deficits/distractibility superimposed on WM impairment in schizophrenia patients.

In the first-degree relatives of schizophrenia patients, a more selective pattern of WM deficits emerged. The tasks in Fig. 1 are ordered based on these findings. Relatives demonstrated impaired performance on verbal and object WM tasks, but not spatial tasks. Further, the tasks in this study that elicited impairment in relatives (i.e., Letter-Number Sequencing, Digit Span Backwards and Object SOP) are ones that meet the D'Esposito et al. (1998) criteria for maintenance-plus tasks, thus suggesting DLPFC involvement. It could be argued that the pattern of deficits in relatives parallels the level of processing demands (i.e., the amount of manipulation/monitoring of information within WM or guarding of information in WM from interference) required by the working memory tasks. On either end of the continuum are tasks provided by D'Esposito et al. (1998) as examples of maintenance-only tasks, a DRT that requires no manipulation of information or guarding of information from interference, and maintenance-plus tasks, a SOP task requiring manipulation of 11 pieces of information. In the middle are tasks that vary in the degree to which they require manipulation of information, with tasks requiring greater manipulation (e.g., Letter-Number Span that requires alphabetization of letters in addition to ordering of numbers) to the right of tasks requiring less manipulation (e.g., Spatial Span Backwards and Digit Span Backwards that only require ordering of numbers).

Thus, the results are consistent with the hypothesis that type of WM processing may be more important than WM domain in eliciting impairment in these relatives, a finding with implications for identifying underlying sites of neuropathology. Retrospectively analyzed from the perspective of the process-specific model, this pattern of WM performance further implicates DLPFC dysfunction in the pathophysiology of and liability for schizophrenia. Alternatively, these findings could be accounted for by the domain-specific model. However, given the intact performance of relatives on spatial WM tasks, interpretation based on this model would suggest compromised VLPFC functioning rather than DLPFC. This conclusion is inconsistent with neuroimaging findings in healthy controls. For example, findings from a PET study using the SOP task in the current study indicated increased blood flow in the DLPFC, not the VLPFC, which correlated strongly with task performance (Curtis et al., 2000). Behavioral, neuroimaging, and neurochemical findings in schizophrenia patients and their relatives are also more consistent with compromised DLPFC.

Functional neuroimaging studies have specifically implicated DLPFC dysfunction in schizophrenia. For example, an early report found that control participants, in contrast to schizophrenia patients, demonstrated increased DLPFC blood flow during completion of the Wisconsin Card Sorting Task (WCST); the DLPFC was the only area of brain activation that differentiated groups (Weinberger et al., 1986). Subsequently, reduced DLPFC activation during *n*-back WM tasks has also been demonstrated in schizophrenia patients, with some evidence for this pattern despite normal performance (Callicott et al., 1998; Carter et al., 1998; Weinberger

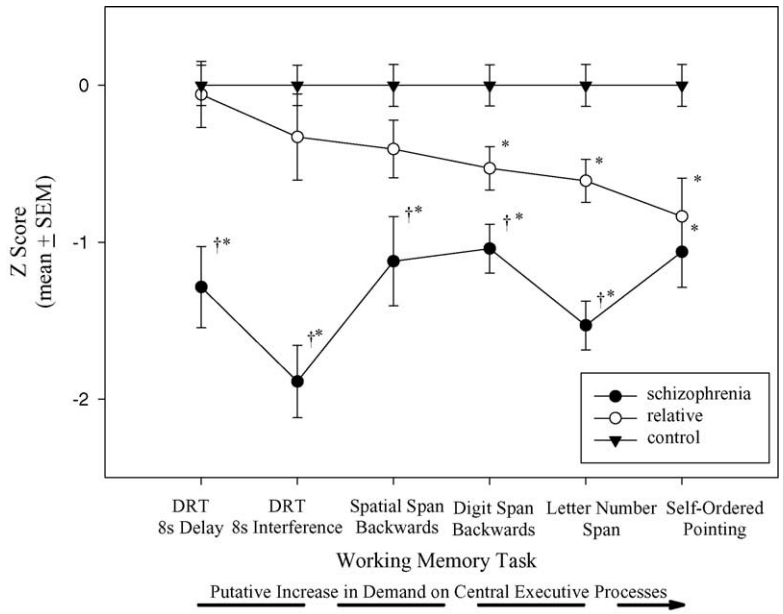

Fig. 1. Working memory performance as a function of increasing processing demands. The symbol '*' differs significantly from control mean, LSD post hoc tests, $p < 0.05$. The symbol '†' differs significantly from relative mean, LSD post hoc tests, $p < 0.05$. Signs were reversed on DRT and self-ordered pointing so lower mean represents worse performance.

et al., 1996). Egan et al. (2001) have proposed a model that ties together genetic liability for schizophrenia, dopamine dysregulation, and DLPFC dysfunction, a model with implications for findings from this study. They found that the presence of the VAL allele of the catechol-*O*-methyltransferase (COMT) gene (an allele associated with increased COMT enzyme activity resulting in reduced PF dopamine availability) in schizophrenia patients and unaffected siblings predicted impaired PF cognition (performance on the WCST) and physiology (DLPFC activation during an *n*-back task) that may explain increased risk for schizophrenia (Egan et al., 2001).

Investigation of the relationship between WM performance and schizophrenia-spectrum psychopathology produced findings less consistent with initial predictions. In schizophrenia patients, there were no significant correlations among WM task performance and negative symptoms. Theoretically, an association among these variables seems likely given the putative role of the frontal lobe in both: however, research findings have been inconsistent. While some researchers have reported significant correlations among negative symptoms and WM performance (e.g., Carter et al., 1996; Glahn et al., 2000; Park, Puschel, Sauter, Rentsh, & Hell, 1999), this has not been a ubiquitous finding (e.g., Fossati, Amar, Raoux, Ergis, & Allilaire, 1999; Stratta et al., 1997). Standardized measures of negative symptoms may need to be modified in order to maximize sensitivity to frontal lobe dysfunction. For example, it has been demonstrated that frontal cortex activation during memory retrieval is differentially affected in patients classified as having deficit versus nondeficit schizophrenia (Heckers et al., 1999). The deficit syndrome of schizophrenia is characterized by the presence of *multiple* negative symptoms that are *enduring* and *not considered secondary* to non-disease factors (e.g., medication status or comorbid depression; Kirkpatrick, Buchanan, McKenney, Alphs, & Carpenter, 1989).

Just as there are inconsistencies in the literature concerning the association of negative symptoms with performance on putative frontal lobe tasks in schizophrenia patients, there are inconsistencies concerning the association of schizotypal traits with performance on putative frontal lobe tasks in their relatives. Some studies have found an association in these relatives (Chen et al., 1998; Franke, Maier, Hardt, & Hain, 1993; Grove et al., 1991; Laurent et al., 2000) but a similar number of studies have failed to find such an association (Franke, Maier, Hardt, Hain, & Cornblatt, 1994; Keefe et al., 1997; Laurent et al., 1999, 2000). In this report, there were no significant correlations among SPQ factors and WM performance, except for a potentially spurious association whereby increased disorganization predicted longer Letter-Number Span. However, dividing the relative group based on the social-interpersonal factor of the SPQ revealed that relatives endorsing a greater number of items performed worse on the SOP task; this task was also most sensitive to WM performance deficits in relatives. Therefore, although the relationship among schizotypal traits and WM performance may not have been as strong as desired, these factors could still represent overlapping sources of vulnerability to schizophrenia. A negative association among recognition memory for faces, SPQ total, and factor scores has previously been reported for the same relative group (Conklin et al., 2002).

These findings have a number of important implications. Potentially the most interesting stems from the finding of WM impairment in unaffected relatives of schizophrenia patients.

This impairment cannot be attributed to factors associated with chronic mental illness, such as lack of motivation or distractibility due to active psychotic symptoms, to medication effects, or to lower education levels. Further, the persistence of these deficits in relatives not meeting diagnostic exclusion criteria indicates that this pattern of WM impairment is not an index of other types of psychopathology but rather an index of the liability for schizophrenia. In contrast to schizophrenia patients, their unaffected relatives were not globally impaired on WM tasks but rather selectively on tasks requiring higher central executive processing. While care must be taken in drawing direct neurophysiological conclusions from behavioral measures that tap multi-faceted cognitive processes, this finding may further implicate DLPFC dysfunction in the pathophysiology of schizophrenia. Elucidation of specific neuropathology associated with schizophrenia can enhance understanding of the origin of psychotic symptoms as well as begin to suggest targeted treatment approaches.

In addition to beginning to unravel the neurophysiology of schizophrenia, the identification of cognitive deficits associated with disorder liability can assist in the search for susceptibility genes. While family, twin, and adoption studies have demonstrated the heritability of schizophrenia, the search for genes has been hindered in part by incomplete genetic penetrance. Both the less than 100% concordance rate for schizophrenia in monozygotic twins (Gottesman, 1991), and the similar disorder risk conferred to offspring of discordant monozygotic twins (Gottesman & Bertelsen, 1989), indicate that there exists non-penetrant carriers among relatives of schizophrenia patients. Having ways to identify these relatives allows researchers to increase the size of informative samples for genetic linkage studies. WM impairment may be a more sensitive indicator of genetic liability for schizophrenia than overt behaviors because the measured performance may be closer to the underlying cause (i.e., neuropathology or genetic variation). Further, relatives exhibiting both WM impairment and schizophrenia-spectrum psychopathology (e.g., schizotypal personality traits) may indicate a subgroup of relatives who carry the greatest genetic risk for schizophrenia.

Finally, many schizophrenia researchers believe that progress in the field has been impeded by diagnostic procedures that identify not only a phenotypically heterogeneous group but also an etiologically heterogeneous group. It may be that neuropsychological deficits could be used in concert with traditional diagnostic approaches to hone in on study samples that are more etiologically homogenous. Neuropsychological assessment, in addition to assessing impairments closer to disorder cause, provides a more objective measure than the subjective evaluation of symptoms from often unreliable patient sources upon which traditional approaches rely. Thus, this combined data approach has a greater probability of identifying individuals that share the same genetic variant predisposing to schizophrenia (see Conklin & Iacono, 2003, for further discussion). It may also be possible to investigate etiological heterogeneity by classifying schizophrenia patients based on the severity of WM impairment (e.g., number of tasks impaired on, magnitude of impairment, and type of processing most affected) and subsequently characterize the performance of relatives for those patients identified as least and most impaired.

A few study findings are worthy of further explanation. First, the failure to find spatial WM impairment on the DRT in our relative sample may appear in conflict with an earlier report by Park et al. (1995). These researchers found first-degree relatives of schizophrenia patients to be impaired on both an oculomotor and a visual-manual DRT. However, their tasks differed on a number of parameters from the task used here. The most relevant difference is the nature of their interference condition. They included interference on all trials, which consisted of determining whether words appearing during the delay belonged to the same semantic category. Their interference task is likely more demanding of central executive processes within WM than the interference task employed here. It may be that inclusion of a more demanding interference condition would have revealed impairment in relatives in this study. Such a finding would be consistent with the process-specific model. An interference task that competes in the same WM domain (i.e., a spatial decision task) might best differentiate groups.

Second, if process is more important than domain in revealing impairment in relatives, it may seem inconsistent that group differences were not revealed on Spatial Span Backwards, which was created as a visual analogue to Digit Span Backwards. We would like to propose that these tasks differ in a critical way other than WM domain. Namely, Spatial Span Backwards includes the Spatial Span Board that can serve as an external cue for participants during the response period. This contrasts with Digit Span Backwards in which the participant must manipulate internal representations and respond without available cues. It may be that these external cues during recall reduce WM load and thus dependence on central executive processes. In fact, other researchers have argued that the board facilitates recall, making Spatial Span Backwards an easier task than Digit Span Backwards (Berch, Krikorian, & Huha, 1998).

Third, there is ongoing debate over how to handle demographic differences that exist between schizophrenia patients and control participants. Arguments against controlling for education rest on the idea that patients and relatives with lower education attainment may be precisely those individuals most neuropsychologically informative. The issue is even more involved when it comes to IQ and WM, as it may be argued that these are largely overlapping constructs. Therefore, removing IQ from WM performance reduces the construct validity of WM tasks and produces findings that are largely uninterpretable. Given that many arguments have been put forth, with no consensus opinion on how to proceed (see Strauss, 2001 for review), statistics both before and after adjusting for demographic variables are provided (see Table 1). Careful examination of the findings with respect to the arguments provided does not detract from the overall WM findings in relatives.

While findings from the current study significantly broaden our understanding of WM function in relatives of schizophrenia patients, there are remaining questions that warrant experimental investigation. For example, research is needed that examines the performance of relatives on tasks from all WM domains, each matched with specific levels of executive processing (e.g., span, *n*-back, and SOP tasks). Across WM domains, tasks should be matched on task characteristics such as modality of presentation (i.e., visual or auditory), method of presentation (e.g., examiner or computer) and number of stimuli to be held in WM, which were free to vary in the current study and may have influenced performance. The domain and process specific models make clear and opposing predictions about performance on such a battery that could provide convergent evidence for the findings herein. Further, WM tasks could be carefully matched for difficulty level. The tasks in this study were not matched on difficulty. However, neuroimaging studies that have matched maintenance-only and maintenance-plus tasks on difficulty have demonstrated dissociation of PFC activation based on invoked executive processes (e.g., Owen, Evans, & Petrides, 1996; Owen et al., 1999).

It is also important to consider the role of stimulus perception, or encoding, in WM performance. Impaired encoding precludes maintenance or manipulation of a stimulus representation within WM. Therefore, WM impairment in schizophrenia could reflect a basic perceptual disturbance thus implicating more posterior brain areas than the PFC. Some studies have indicated that WM deficits in schizophrenia disappear when stimulus encoding is equated across groups (e.g., Javitt, Strous, Grochowski, Ritter, & Cowan, 1997). Subsequently, researchers have found WM deficits in schizophrenia patients after systematically adjusting for *individual* encoding differences (Wexler, Stevens, Bowers, Sernyak, & Goldman-Rakic, 1998; but see Javitt et al., 2000 for contrary results). In the current study, there is evidence for WM deficits in the context of adequate encoding, as evidenced by group differences on the DRT 8 s delay and 8 s interference conditions despite comparable group performance on the 0 s control and 0.5 s delay conditions. Further, in prior published work (i.e., Conklin et al., 2000), relatives of schizophrenia patients were impaired on backward but not Forward Digit Span Tasks, suggesting that stimuli perception was not the only compromised process. Perceptual processing difficulties identified in schizophrenia patients (e.g., Javitt et al., 1997) have not been demonstrated in their well relatives. Therefore, within the relative group, the susceptibility to encoding deficits may be even less of a threat to WM findings. That being said, future studies should ensure that subjects have met the perceptual demands of WM tasks, particularly object working memory tasks as this domain may be especially vulnerable to encoding effects (Tek et al., 2002).

Neurodevelopmental models of schizophrenia are emerging that provide a unifying framework for diverse lines of research (see Conklin & Iacono, 2002 for review). In part, these models propose that a brain "lesion" occurring early in life lies dormant until normal maturational events trigger the onset of psychosis (e.g., Weinberger, 1987). The PFC is a brain area that is believed to be developing throughout adolescence. Therefore, it would be useful to consider the cognitive performance of typically developing children on a battery of frontal lobe sensitive tasks and compare longitudinal performance to children at risk for schizophrenia. Current findings predict that high-risk children would demonstrate impaired performance relative to control participants, given that they are first-degree relatives of schizophrenia patients. However, it is unclear whether this divergence in performance would predate or parallel the onset of psychotic symptoms in high-risk children who later develop schizophrenia. If this performance deficit predates psychosis, it may serve as an indicator for prophylactic treatment.

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