Spatial working memory deficits in adolescents at clinical high risk for schizophrenia

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Abstract

Identifying endophenotypic markers is crucial to schizophrenia research for finding appropriate preventive strategies. Working memory (WM) deficit has been suggested as a marker for schizophrenia but its presence in adolescents at high risk is understudied. We piloted a test of spatial WM function in adolescents at clinical high risk (CHR) for schizophrenia and in age- and IQ-matched low-risk control subjects. CHR adolescents showed deficits in spatial WM compared with controls but showed intact performance on a non-WM-demanding spatial control task. Although based on a small pilot study, the results strongly suggest that WM deficit may be a risk factor for psychosis.

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1. Introduction

Working memory (WM) is an active short-term memory system (Baddeley, 1986). A majority of schizophrenia patients (SZ) show WM deficits that transcend the differences in specific paradigms or tasks employed (see Lee and Park, in press for review). WM deficits are present in unmedicated SZ (Carter et al., 1996), but not in bipolar subjects taking antipsychotic drugs (Park and Holzman, 1992, 1993; Gooding and Tallent, 2001; Glahn et al., in press). WM deficits have been observed in clinically unaffected, medication-free relatives of SZ (Park et al., 1995b; Myles-Worsley and Park, 2002; Conklin et al., 1995; MacDonald et al., 2003) as well as in schizotypal subjects (Park et al., 1995a; Park and McTigue, 1997; Tallent and Gooding, 1999). In addition to having an elevated risk for schizophrenia, many high-risk subjects show biobehavioral abnormalities similar to those found in SZ. (Holzman and
Matthysse, 1990; Cornblatt and Keilp, 1994). Furthermore, past studies of genetic high-risk children suggest that neurocognitive probes may be very useful in predicting the onset of psychosis, especially tasks that assess attention and WM (Cornblatt, 2001).

The first episode of schizophrenia typically presents itself during early adulthood but a long prodromal period often precedes it and some signs may even be detected in childhood (Erlenmeyer-Kimling et al., 2000, Walker et al., 1994). Recent prodromal studies have found cognitive deficits similar to those marking affected patients, but of lesser magnitude, including deficits in attention, executive function and WM (Lencz et al., in press; Woods et al., 2003; Hawkins et al., 2004). These cognitive markers may aid in the prediction of psychosis in prodromal individuals (Lencz et al., in press).

WM deficit is a good candidate as the endophenotypic marker for schizophrenia and may help detect possible signs of schizophrenia in individuals at risk. One question that needs to be addressed is whether children at risk show deficits in WM and if they do, whether these deficits yield potentially good markers for predicting future psychosis.

In the present study, WM function in adolescents at clinical high-risk for schizophrenia and matched control subjects was pilot-tested using the delayed response task (DRT), which has been used to elucidate the neural correlates of WM (see Park and Lee, 2002 for review). We focused on clearly prodromal, clinically high-risk children using strict inclusion criteria (Cornblatt, 2002).

2. Methods

2.1. Participants

Subjects for this pilot study of the role of spatial WM in clinical high-risk (CHR) adolescents were consecutive admissions to the Recognition and Prevention (RAP) Program, which studies clinical and cognitive aspects of the schizophrenia prodrome (Cornblatt, 2002; Lencz et al., 2003, 2004). Eight CHR subjects were selected on the basis of attenuated positive or negative symptoms rated on the Scale of Prodromal Symptoms (McGlashan et al., 2001; Miller et al., 1999, 2002). Seven CHR subjects had DSM-IV diagnoses including anxiety disorders (n=4), depressive disorders (n=2), and ADHD (n=2). Comorbidity is common in prodromal adolescents (Lencz et al., 2004) but our sample size is too small to determine the effect of comorbidity on WM function.

Ten normal controls were also recruited via advertisements in the community surrounding Hillside Hospital, NY and Evanston, IL. Controls were not excluded for non-psychotic Axis I disorders in themselves or their first-degree relatives. None of the control subjects had current diagnosable Axis I disorders, but one had depressive disorder NOS, in full remission.

Written informed consent was obtained from the subject if >17 years old, or from the parent (with the subject’s written assent) if under 18. No subject had a history of head injury, neurological disorder or diagnosed substance abuse. Diagnoses were obtained using KSADS-E (Orvaschel and Puig-Antich, 1994).

The two groups did not differ significantly in age (F(1,16)=0.05, p>0.82); education (F(1,16)=0.31, p>0.58), IQ estimated using Vocabulary and Block Design subscales of the WISC-III for subjects under 16 years (Sattler, 1992), and from WAIS-R for subjects 16 and older (Brooker and Cyr, 1986) (F(1,16)=0.39, p>0.54); SES estimated by Hollingshead (1957) (F(1,15)=0.88, p>0.36); or the proportion of women (Chi square =2.21, p>0.13). See Table 1.

2.2. Procedure

Subjects were given instructions and practice trials first.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Mean (SD) of demographic variables and WM performance of high- and low-risk groups</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>High risk (N=8)</td>
</tr>
<tr>
<td>Age</td>
<td>16.3(2.6)</td>
</tr>
<tr>
<td>Education</td>
<td>10.4(2.5)</td>
</tr>
<tr>
<td>IQ</td>
<td>108.8(16.1)</td>
</tr>
<tr>
<td>Female (%)</td>
<td>0</td>
</tr>
<tr>
<td>WM task error distance</td>
<td>29.4(16.6)</td>
</tr>
<tr>
<td>Control task error distance</td>
<td>8.6(3.4)</td>
</tr>
<tr>
<td>Number of WM errors</td>
<td>9.0(3.9)</td>
</tr>
<tr>
<td>Number of control task errors</td>
<td>0(0)</td>
</tr>
</tbody>
</table>
2.2.1. Spatial WM task

Subjects fixated at a small dot at the center of a Macintosh computer screen. When ready to start, they brought the cursor of the mouse to the central fixation dot and clicked the mouse to initiate a trial. The trial consisted of a target (black circle of 20 pixels in diameter) appearing in the periphery of the screen for 200 ms immediately followed by a 10-s delay period. During the delay, the subject was required to do an intervening task that prevents idiosyncratic rehearsal strategies and insures that the subject fixates at the center. This intervening task involved observing a series of squares that appear at the fixation point and noting when they change in size (i.e., grow bigger or smaller). The squares were presented at a rate of one per second. After the delay, the fixation dot and 16 black circles were shown. Subjects were asked to remember the location of the target and move the mouse to the correct location. They were asked to be as accurate and as fast as possible. The coordinates of the mouse position and the response time were recorded. Detailed descriptions of the task are found in earlier papers (Park and McTigue, 1997; Park et al., 1999; Myles-Worsley and Park, 2002, see Fig. 1 for a schematic diagram of the procedure).

2.2.2. Spatial control task

To control for the sensorimotor component of the spatial WM task, a control task requiring spatial location detection but not WM was conducted. This task was identical to the spatial WM task except that there was no delay period. Subjects fixated at the center and, when ready, they brought the mouse cursor to it and clicked it to start a trial. A black circle (target) was flashed for 200 ms. Immediately afterwards, 16 black circles appeared on the screen. Subjects moved the mouse to the correct target location as accurately and quickly as possible. The coordinates of the cursor position and the response time were recorded see (see Fig. 1).

Intact performance on the sensory control task, coupled with poor performance on the spatial WM task, would rule out the possibility of a deficit in the sensorimotor performance.

There was one block of 32 spatial WM trials and one block of 32 spatial control trials. The order of presentation of the blocks was counterbalanced across subjects.

2.2.3. Scoring

Error distance (in pixels): the distance between the center of the target position and location indicated by the subject (the mouse cursor position) was computed from $x, y$ coordinates. Error distance of zero would indicate perfect performance.

Number of errors: a response was scored as correct if the error distance was $<$20 pixels.

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Fig. 1. Procedure for the spatial WM and spatial control task.
3. Results

3.1. Error distance

A repeated measures ANOVA showed a main effect of group ($F(1,16)=6.13, p<0.025$). The CHR group showed increased spatial WM error distance (almost double) compared with the low-risk group ($F(1,16)=5.62, p<0.031$). But on the control task, the two groups did not differ ($F(1,16)=1.20, p>0.29$). There was also a main effect of the task type ($F(1,16)=36.40, p<0.001$). Both groups performed better on the control task than on the WM task. An interaction between risk group and task type approached significance ($F(1,16)=4.16, p=0.058$) such that the difference in performance on the WM task compared with the control task was greater for the CHR group.

3.2. Number of errors

On the spatial control task, no subject made any errors. ANOVA indicated a significant group difference on WM accuracy ($F(1,16)=15.90, p<0.001$). CHR subjects made on average 9.0 errors (SD = 3.85) whereas low-risk subjects made 3.1 errors (SD = 2.37, see Table 1).

4. Discussion

We found WM deficits in adolescents at clinical high risk for schizophrenia who were matched in age and IQ to low-risk subjects. This report is the first to use the DRT in a prodromal population, and is a replication of spatial WM findings using different measures (Hawkins et al., 2004, Woods et al., 2003). Identification of potential endophenotypic markers is of utmost importance to psychiatric research if we are to identify those at risk for schizophrenia before the first psychotic episode and find appropriate preventive treatment strategies to reduce the severity of later symptoms (Cornblatt, 2002). Attentional abnormalities and social dysfunction (Freedman et al., 1998) and verbal learning deficits (Lencz et al., in press) seem to be related to later psychosis. These potential markers are now joined by a neurobiologically circumscribed function, that of WM. By utilizing what we know about neurocognitive abnormalities in schizophrenia, we may be able to define a potential endophenotypic profile, using multiple measures which may increase the likelihood of predicting illness onset.

Although the sample size of this study is small, the subjects were carefully selected following strict inclusion criteria and rigorous procedures. Given the relatively large effect of the WM deficit in the high-risk group, more extensive future studies with larger sample sizes are warranted.

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