

Spatial Working Memory Deficits in Schizophrenia Patients and Their First Degree Relatives From Palau, Micronesia

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Spatial working memory deficits associated with dorsolateral prefrontal dysfunction have been found in Caucasian samples of schizophrenia patients and their first-degree relatives. This study evaluated spatial working memory function in affected and unaffected members of multiplex schizophrenia families from the Republic of Palau to determine whether the spatial working memory deficits associated with schizophrenia extend to this non-Caucasian population. Palau is an isolated island nation in Micronesia with an elevated prevalence of schizophrenia and an aggregation of cases in large multigenerational families. Our objective was to evaluate the potential for spatial working memory function to serve as one of multiple endophenotypes in a genetic linkage study of these Palauan schizophrenia families. A spatial delayed response task requiring resistance to distraction and a sensorimotor control task were used to assess spatial working memory in 32 schizophrenia patients, 28 of their healthy first-degree relatives, and 19 normal control subjects. Schizophrenia patients and their relatives were significantly less accurate than normal control subjects on the spatial delayed response task but not on the sensorimotor control task. On both tasks, patients and relatives were slower to respond than the normal controls. There were no age or

gender effects on accuracy, and working memory performance in schizophrenia patients was not significantly correlated with medication dosage. In summary, spatial working memory deficits that have been found in Caucasian schizophrenia patients and relatives were confirmed in this isolated Pacific Island family sample. These results suggest that spatial working memory deficits may be a potentially useful addition to the endophenotypic characterization of family members to be used in a comprehensive genome wide linkage analysis of these Palauan families. © 2002 Wiley-Liss, Inc.

KEY WORDS: schizophrenia; spatial working memory; neurocognitive dysfunction; endophenotype; family study; genetics

INTRODUCTION

Schizophrenia is a complex brain disorder associated with impairment in multiple cognitive domains. Family, twin, and adoption studies have clearly established a significant genetic component in the etiology of schizophrenia [Gottesman et al., 1982, 1987; Gottesman, 1991; Kendler and Diehl, 1993]. Finding susceptibility genes for schizophrenia using a disease phenotype, however, has proven to be remarkably difficult. One promising strategy that has been advocated for genetic studies of schizophrenia is to broaden the phenotypic characterization of subjects to include discrete neurobiological traits associated with the illness [Matthysse et al., 1986; Tsuang, 1993; Faraone et al., 1995; Moldin and Gottesman, 1997; Freedman et al., 1999; Baron, 2001]. Many first-degree relatives who remain clinically unaffected throughout their lives show impairments in neurobiological functioning similar to those found in schizophrenia patients. These impairments may be “endophenotypes” for schizophrenia, neurobiological traits that reflect an underlying genetic liability for schizophrenia and can thus identify unaffected relatives

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who are carriers of a genetic liability for the illness [Gottesman and Shields, 1972; Gottesman et al., 1982].

Neurophysiological traits such as P50 sensory gating [Freedman et al., 1997, 1999] and ocular motor dysfunction [Holzman et al., 1988; Grove et al., 1992; Arolt et al., 1996] have been studied by several research groups as possible endophenotypes for schizophrenia. In addition, certain cognitive deficits such working memory have emerged as potential candidates because they may be able to meet crucial criteria for an endophenotypic trait. To qualify as an endophenotype for schizophrenia, a neurobiological abnormality must occur at a significantly higher rate not only in schizophrenia patients but also in their unaffected first-degree relatives compared to normal controls. When a cognitive deficit found in schizophrenia patients extends to their unaffected first-degree relatives, this indicates that the abnormality is familial and could be genetically related to risk for schizophrenia.

Working memory is a limited-capacity system that maintains information in a buffer so that the contents are available for attentional processing when a response based on that content is required [Baddeley, 1986, 1992, 1996]. When the working memory system is intact, distracting stimuli may be registered but do not interfere with attentional processing. Thus, working memory serves to inhibit or suppress task-irrelevant responses and competing processes, thereby minimizing distractibility and maintaining the focus of attention on task-relevant stimuli.

The cognitive problems reported by schizophrenia patients include distractibility, difficulty focusing, an inability to screen out irrelevant information, and feeling overloaded with too many stimuli at the same time [McGhie and Chapman, 1961; Freedman and Chapman, 1973]. From a functional perspective, the cognitive problems described by schizophrenia patients suggest a fundamental inhibitory dysfunction expressed by deficits on cognitive tasks that require reliance on working memory and resistance to distraction. Research has shown that tasks that require inhibitory processing such as delayed response tasks and the antisaccade task have been associated with dysfunction in the dorsolateral prefrontal cortex [Fuster, 1973, 1980; Guitton et al., 1985; Goldman-Rakic, 1987, 1990; Funahashi et al., 1989, 1990, 1991; Pierrot-Deseilligny et al., 1991a,b, 1995; Gaymard et al., 1998a,b]. A recent fMRI study of visual working memory by de Fockert et al. [2001] suggests that working memory activity in the prefrontal cortex plays an essential role in resistance to distraction. Therefore, working memory dysfunction may be able to serve as a measurable expression of a specific neurobiological disruption in prefrontal cortex that represents an endophenotypic marker for schizophrenia.

A number of different approaches have been used in schizophrenia research to measure working memory. The digit span test [Erlenmeyer-Kimling and Cornblatt, 1992] and more difficult variations on the digit span such as the letter-number task [Gold et al., 1997] have been widely used to assess working memory performance. The neural correlates of digit span performance are not well understood, however, and these digit span

tests do not include an assessment of resistance to distraction. A potentially more informative test of working memory is the delayed response task (DRT) that can be specifically adapted to measure spatial working memory performance with distraction. The DRT paradigm that has been used as a laboratory task since the early 1900s [Hunter, 1913] is well suited for studies of spatial working memory. Neurophysiological studies using the DRT with non-human primates have shown that the dorsolateral prefrontal cortex plays a crucial role in the maintenance of spatial representation during a delay period [Goldman-Rakic, 1987].

Park and Holzman [1992] used the DRT to study spatial working memory in schizophrenia patients and later in the first-degree relatives of schizophrenia patients [Park et al., 1995]. In this task, visual stimuli (circles) are presented as targets and the subject is required to remember the location of a target circle and respond to that location after a delay period during which a distractor task must be carried out. Because nonverbal stimuli are used, performance is independent of language ability and the task corresponds closely with the DRT used in neurophysiological studies of non-human primates. Spatial working memory deficits are present in patients with schizophrenia whether they are symptomatic or in remission [Park and Holzman, 1992, 1993; Park et al., 1999], and these deficits also occur in the nonpsychotic first-degree relatives of schizophrenia patients [Park et al., 1995]. The presence of spatial working memory deficits in healthy relatives of schizophrenia patients suggests a neurobiological abnormality that is familial and independent of treatment effects.

The purpose of our study was to determine whether abnormal spatial working memory performance extends to a non-Caucasian sample of families from Palau, Micronesia who are participating in a genetic linkage study of schizophrenia. We have been evaluating several potential neurobiological traits as possible endophenotypes including P50 sensory gating [Myles-Worsley et al., 1998; Myles-Worsley, in press] and antisaccade performance [McDowell et al., 1999]. The addition of spatial working memory deficits to our endophenotypic characterization of family members may increase the power of future genetic linkage studies of these families.

The Republic of Palau is a geographically and ethnically isolated island nation in Micronesia where the lifetime prevalence of schizophrenia is approximately double the worldwide rate and cases cluster in large multigenerational families [Myles-Worsley et al., 1999]. Palau offers unique advantages for studying neurobiological endophenotypes for schizophrenia. Because the large Palauan schizophrenia families combine multiple affected sibships linked by a common founder, an unaffected family member can represent a first-degree relative of one schizophrenia patient as well as a more distant relative (e.g., aunt/uncle, first cousin) of other schizophrenia patients in the extended family. Therefore, these relatives may carry a higher genetic risk for schizophrenia than first-degree relatives in simplex families and may be more informative for subsequent linkage studies using neurobiological endophenotypes.

We compared schizophrenia patients to unaffected first-degree relatives and normal control subjects to determine whether spatial working memory deficits in schizophrenia patients and their relatives extend to this isolated non-Caucasian population. Our objective was to evaluate the ability of spatial working memory performance to serve as an endophenotype in a genetic linkage study of Palauan schizophrenia families.

MATERIALS AND METHODS

Subjects

Subjects who were recruited from an already ascertained Palauan sample [Myles-Worsley et al., 1999] included 32 schizophrenia patients (12 females), 28 first-degree relatives of schizophrenia patients (18 females), and 19 normal control subjects (12 females). Although we studied only one schizophrenia patient per nuclear family, six of the 32 patients had a fourth- or fifth-degree relative with schizophrenia who also participated, a reflection of the complex interconnections that characterize the extended multigenerational families found in Palau. The other 26 patients were more distantly related. Only one first-degree relative per patient was studied. All subjects were between 25 and 65 years of age.

Patients and relatives were diagnosed based on a modified Schedule for Affective Disorders and Schizophrenia–Lifetime Version (SADS-L) [Endicott and Spitzer, 1978] conducted by a U.S. trained, board certified psychiatrist (William Byerley, MD) supplemented by a review of psychiatric medical records. Consensual diagnoses based on Research Diagnostic Criteria [Spitzer et al., 1978] were established by an expert diagnostic panel as reported previously [Myles-Worsley et al., 1999]. Only patients with narrowly defined schizophrenia or schizoaffective disorder (mainly schizophrenic course) were included in the present study. Relatives diagnosed with an Axis I DSM-III-R disorder were excluded. All patients were on therapeutic doses of typical antipsychotics (predominantly haloperidol and fluphenazine).

Normal control subjects were recruited from families identified as unaffected during the ascertainment phase of the epidemiological study. To qualify, subjects were required to be free of any Axis I DSM-III-R psychiatric disorder and any chronic neurological disease and to have no first-, second-, or third-degree relatives with a psychotic illness. The latter qualification was fulfilled by conducting a FIGS interview (Family Interview for Genetic Studies) with the subject and at least one other family informant.

Subjects showing evidence of chronic substance abuse were excluded. To recruit as many qualifying subjects in each category as possible, we made no attempt to match the subjects in each group for age or gender. Among Palauan schizophrenia patients, we previously reported a 2:1 male:female ratio and an earlier age of illness onset for males vs. females [Myles-Worsley et al., 1999]. These epidemiological characteristics of the illness in Palau were reflected in a higher proportion of male subjects in

the total patient group (62.5%) compared to both the relatives (35.7%) and the normal group (36.8%) and a younger mean age for the patients (38.5 years, SD = 6.56) compared to the relatives (48.0 years, SD = 11.5) and the normal subjects (43.0, SD = 12.3).

Study procedures were approved by the Institutional Review Boards of the University of Utah and the Republic of Palau. All participants provided written informed consent after receiving a thorough explanation of the study in both English and Palauan.

Procedure

Subjects were seated at a table facing a Macintosh notebook computer. Subjects were first given an opportunity to practice using the mouse to move the arrow cursor. To familiarize each subject with the task and instructions, there were practice trials before actual testing began. Spatial working memory was assessed using two tasks, a sensorimotor control task followed by a spatial delayed response task, both of which are presented schematically in Figure 1.

Sensorimotor control task. A task requiring basic spatial target detection was first administered to screen subjects for ability to respond according to instructions and control for potential sensorimotor performance disabilities. Subjects were instructed to focus their eyes

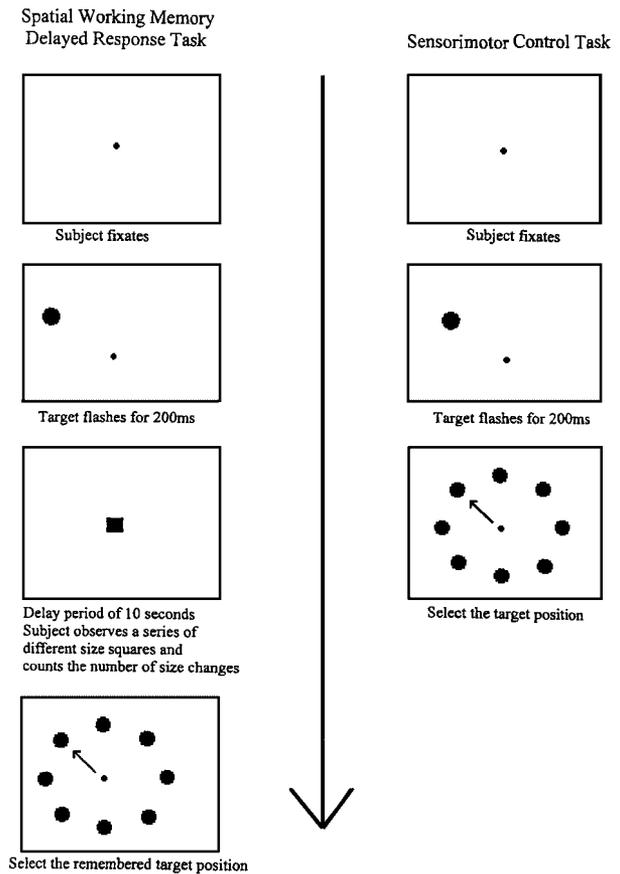


Fig. 1. Schematic diagram of the spatial working memory delayed response task (DRT) and the sensorimotor control task.

on a central fixation point and when they were ready to begin, they were instructed to move the cursor to the central fixation point and click the mouse to initiate a trial. When the mouse was clicked, a target (black circle) appeared on the screen for 200 msec, immediately followed by a screen presenting eight black circles arranged in a circular pattern. Subjects were instructed to move the mouse to the correct target and click once, as quickly and accurately as possible. The coordinates of the mouse position and response latency were recorded. All recruited subjects 65 years of age and younger were able to complete the sensorimotor control task.

Spatial delayed response task. The working memory task was identical to the sensorimotor control task except there was a delay with distraction between the appearance of the target and the response screen. Subjects were again instructed to focus their eyes on a central fixation point and to move the cursor to the central fixation point and click the mouse to initiate a trial. When the mouse was clicked, a target (black circle) appeared on the screen for 200 msec. Immediately after the target presentation, there was a 10-sec delay period, during which the subject observed a series of squares at the fixation point. The size of the square changed at random intervals during the delay period and the subjects were asked to count the number of changes in size (from 4–7). After this delay period, the fixation point and eight black circles arranged in a circle appeared on the screen. Subjects were required to move the mouse to the remembered position of the target and click once, as quickly and accurately as possible.

There were 16 sensory control trials followed by 16 memory trials. On each trial, the coordinates of the mouse position and the response latency were recorded. Accuracy was assessed by calculating the error distance for each trial defined as the distance between the x,y coordinates of the center of the target circle and the x,y coordinates of the mouse, and a mean error distance score over 16 trials was computed for each task. In addition, the mean response latency of the 'correct' trials was compared across groups. The criterion for correct performance was an error distance less than 25 pixels because the target itself had a radius of 20 pixels. Mean

correct response latency over 16 trials was computed for each task.

RESULTS

Table I presents the means and standard deviations for the two main measures, error distance and response latency for the sensorimotor control task and the working memory DRT and effect sizes when patients and relatives were compared to normal controls. For each of these dependent variables, a repeated-measures analysis of variance (ANOVA) was conducted to compare performance on the two tasks across groups, and t -tests were used for specific comparisons.

For the error distance measure, there were significant main effects for diagnostic group ($F=6.37$, $df=2,76$, $P<0.003$) and type of task ($F=38.97$, $df=1,76$, $P<0.0001$) and a significant group by task type interaction ($F=7.59$, $df=2,76$, $P<0.001$). All three groups performed with similar accuracy on the sensorimotor control task, but when subjects were required to perform the working memory DRT, mean error distance increased most for the schizophrenia patients, less for the relatives, and least for the normal controls. Although the effect size for the error distance performance measure was considerably greater for schizophrenia patients than for relatives (5.0 vs. 1.0), both the patient and relative groups showed spatial working memory deficits relative to control subjects, and these deficits occurred in the absence of deficits in spatial target detection. Intact performance on the sensorimotor control task served to rule out the possibility of a generalized deficit in task performance in schizophrenia patients.

In the case of response latencies for the three groups on the working memory and the control tasks, there was a main effect of diagnostic group ($F=5.25$, $df=2,76$, $P<0.007$) and a main effect of task type ($F=42.35$, $df=1,76$, $P<0.0001$), but there was no group by task type interaction. Specific comparisons showed that on the sensorimotor task and the working memory DRT, patients were slower than relatives who were slower than normal subjects. All subjects were slower on the working memory DRT than the control task.

TABLE I. Error Distance and Response Latency on the Sensorimotor Control Task and the Working Memory Task by Group

	Error Distance (pixels)		Response Latency (msec)	
	Sensorimotor control task	Working memory task	Sensorimotor control task	Working memory task
Schizophrenia patients				
Mean	9.33	47.38	5122	7354
SD	9.27	46.45	3383	3280
Effect size ^a	0.52	5.03	2.27	0.79
First-degree relatives				
Mean	9.08	23.53	4073	5888
SD	5.89	11.00	2789	3899
Effect size ^a	0.43	1.00	1.37	0.36
Normal controls				
Mean	7.90	17.60	2468	4655
SD	2.73	5.91	1168	3434

^aEffect size = (mean for group – mean for normals)/SD for normals.

Figure 2 presents the distribution of error distance scores for the working memory DRT in each of the three groups. No normal subjects exceeded a mean error distance of 28 pixels (8 pixels outside the circumference of the target circle). If this maximum is considered the cutoff for normal performance, the results show that 53% of schizophrenia patients and 25% of their first degree relatives carried out less accurately than any of the normal Palauan subjects.

In the patient group, Pearson correlations showed no significant effect of medication dosage (measured in chlorpromazine equivalent units) on any of the control task or working memory DRT measures. Furthermore, none of the measures showed significant main effects of gender or a group-by-gender interaction.

When age was evaluated as a covariate, there were significant effects on response latency but not on response accuracy as measured by error distance. Response latency on both the sensorimotor control task and the working memory DRT covaried with age: the older the subject, the longer the latency to respond. Because aging is associated with a decline in working memory function

[Salthouse and Skovronek, 1992; Baddeley et al., 1999] and the patients were younger than the normal controls, the effects of age would be expected to impair the performance of the older normal controls relative to the younger schizophrenia patients. In the present study with subjects 25–65 years old, however, the age factor did not significantly influence spatial working memory accuracy and the younger schizophrenia patients were clearly more impaired than the older normal subjects. Although older subjects were slower to respond, they were just as accurate as younger subjects.

DISCUSSION

The objectives of our study were to determine whether the spatial working memory deficits found in Caucasian samples of schizophrenia patients and their first-degree relatives extend to schizophrenia families from an isolated Pacific Islander population. If so, this would lend support for the use of spatial working memory function as a potential endophenotype in a genetic linkage study of these families. Spatial working memory deficits that have been found in Caucasian schizophrenia patients and relatives were confirmed in this Palauan sample. This confirmation of a similar pattern of deficits in a non-Caucasian sample is important because schizophrenia is phenomenologically similar worldwide and the underlying neurobiological disruptions associated with the illness should apply across ethnic groups.

Although our sample sizes in each diagnostic group are too small to confidently estimate relative risk, the results show that 53% of schizophrenia patients and 25% of their first degree relatives performed less accurately than any of the normal Palauan subjects. Therefore, the relative risk for abnormal spatial working memory in this Palauan sample may be sufficiently high to warrant its inclusion in the endophenotypic linkage study we plan to conduct in these multiplex schizophrenia families.

In the same Palauan family sample, Myles-Worsley et al. [1998] in press, found P50 sensory gating deficits as measured by the auditory evoked potential paradigm in 65% of schizophrenia patients and 50% of their first-degree relatives versus only 10% of normal controls, indicating that the P50 sensory gating deficit, another sign of inhibitory dysfunction, qualifies as a potential endophenotype for schizophrenia in this sample. Furthermore, Allen et al. [1996] reported that schizophrenia patients from Palau as well as New Guinea and New Zealand showed deficits in anti-saccade performance, similar to the deficits observed in other countries. In a subsequent study, McDowell et al. [1999] reported impaired anti-saccade performance in 68% of Palauan schizophrenia patients and 54% of their first-degree relatives compared to only 1% of Caucasian normal controls. Thus, anti-saccade performance also shows considerable promise as an endophenotype for schizophrenia in these Palauan families. The presence of spatial working memory deficits as well as poor anti-saccade performance in the healthy relatives suggests that there may be subtle abnormalities of the dorsolateral prefrontal system in these individuals who may

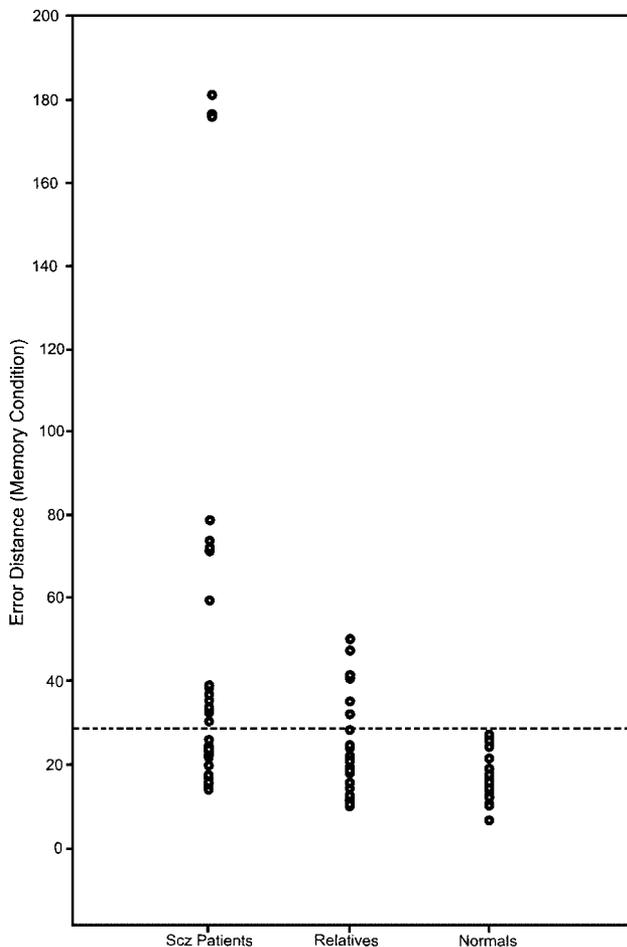


Fig. 2. Distribution of error distance scores on the working memory DRT for schizophrenia patients, first-degree relatives and normal control subjects.

carry a latent liability for schizophrenia even though they do not display clinical symptoms.

In summary, the spatial working memory deficits that we have identified in these Palauan schizophrenia families represent one more potential endophenotypic marker for a genetic linkage study of these families. Using a constellation of measures such as spatial working memory plus anti-saccade performance to assess disruptions in prefrontal cortex combined with P50 sensory gating to assess a subcortical inhibitory dysfunction may improve our ability to identify unaffected relatives who carry a liability for schizophrenia. By including multiple endophenotypes in our linkage analyses, we hope to ultimately identify susceptibility loci that are more directly relevant to the functional neurobiological impairments that characterize schizophrenia.

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