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The Stability of Inhibitory and Working Memory Deficits in Children and Adolescents Who are Children of Parents With Schizophrenia

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Cognitive deficits are a central feature of schizophrenia and occur in first-degree relatives of schizophrenic probands, even in the absence of psychotic symptoms. A number of cognitive domains have been implicated including measures of response inhibition and working memory. While the stability of cognitive deficits has been demonstrated in individuals with schizophrenia, stability of deficits has not been explored in first-degree relatives. This report focuses on 25 children (ages 6–15 years), all with at least one schizophrenic parent. The children were assessed twice, utilizing inhibitory and working memory tasks, with a mean 2.6 years between visits. Stop reaction time (a measure of motor inhibition) and performance on a counting span task (a measure of verbal working memory) were borderline to mildly impaired (compared with a typically developing comparison group) at both visits with similar effect sizes (stopping task time 1, effect size = 0.46, time 2 effect size = 0.50; counting span time 1 effect size = 0.53, time 2 effect size = 0.42). For these 2 tasks, individual age-adjusted scores also correlated across both time points (r = 0.41–0.76) suggesting that individual children maintained deficits across time. As etiologically driven strategies are developed for the cognitive deficits of schizophrenia, expansion of these treatments to relatives who share the cognitive but not the psychotic symptoms may be worth exploring.

Key words: schizophrenia/inhibition/working memory

Schizophrenia has long been proposed as a neurodevelopmental disorder, where the disease is caused by alterations in brain development that precede, sometimes by years or decades, the onset of diagnostic symptomology.[1] This neurodevelopmental hypothesis has been supported by the finding of neuropsychological deficits in genetically high-risk children, eg, children who are not psychotic but are born to a schizophrenic parent (results across laboratories are well summarized by Seidman et al[2]). While deficits can be identified across a variety of cognitive domains, the largest effects are seen in tasks involving behavioral inhibition, spatial working memory, a combination of inhibition and working memory or in verbal ability.[2–4] The working memory and inhibitory deficits found in genetically high-risk children and adolescents is similar to that seen in nonpsychotic adult first-degree relatives of schizophrenic probands.[5–7]

Longitudinal studies of neuropsychological function conducted on individuals affected with schizophrenia conclude that cognitive deficits are relatively stable over the course of the illness[8,9]; yet there is little literature to date that assesses the stability of cognitive deficits in first-degree relatives. This report focuses on the stability of deficits in working memory and inhibition in children with a schizophrenic parent.

Methods

Participants

An initial sample of 51 children (33 males, 18 females; age range = 6–16 years) who had at least one parent meeting *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (*DSM-IV*), criteria for schizophrenia were initially assessed on a variety of neuropsychological tasks.[10] Details on recruitment of the initial sample as well as results from that initial assessment have been previously reported.[11] The oldest subjects in the initial sample had passed out of the age range of interest (upper limit of 19 years) at the time of the follow-up study and were not asked to return. Twenty-five subjects (49%) returned after a mean of 2.6 ± 1.1 years for repeat testing. At the time of initial recruitment, the recruitment strategy consisted of identifying parents with schizophrenia and then recruiting their children. This limited the risk of ascertainment bias toward more psychiatrically ill children, and thus, all children were included in the analysis irrespective of symptomology. Four of the subjects presented

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with schizophrenia-spectrum illnesses at the time of the initial assessment; one subject developed psychosis between the first and second visits. Axis I psychiatric diagnoses are common in children with a schizophrenic parent,[12] and, based on a structured interview[13] at the first visit, 68% of the children in this sample met diagnostic criteria for an Axis I diagnosis, including attention-deficit hyperactivity disorder (ADHD) (n = 11, 44%), simple phobia (n = 4, 16%), generalized anxiety disorder (n = 3, 12%), major depression (n = 2, 8%), social phobia (n = 2, 8%), encopresis (n = 2, 8%), adjustment disorder (n = 2, 8%), enuresis (n = 1, 4%), nonalcohol substance abuse (n = 1, 4%), and chronic tic disorder (n = 1, 4%). None of the subjects used tobacco. This frequency of nonpsychotic illness is similar to that seen in the portion of the sample who did not return at the second visit. Subjects who returned for a second visit did not differ from subjects who did not return on age (t = 1.7, P = .10), gender (χ^2 = 0.12, P = .77), ethnicity (Caucasian vs non-Caucasian; χ^2 = 0.12, P = .73), or block design–standardized scores (t = 0.5, P = .61). Mean age ± SD for the genetically at-risk group at the first visit was 9.8 ± 2.9 years and at the second visit was 12.4 ± 2.8 years.

The neuropsychological tests chosen for this study are without norms. In order to adjust for age, a typically developing group was recruited. This group consisted of 82 children with no personal history of psychotic or neurological disorders and no family members, out to third-degree relatives, with a known psychotic disorder. Pedigrees were drawn from information provided by parents. Mean age for the typically developing group was 11.1 ± 2.8 years. All children involved in the study were administered the Schedule for Affective Disorders and Schizophrenia for School Age Children—Present and Lifetime Version.[13] Exclusion criteria for the typically developing group were limited to children with a known neurological disorder or current illicit substance use. Because there is a high frequency of mental illness in the general population, children in this group were not excluded if they met criteria for a nonpsychotic *DSM-IV* Axis I diagnosis.[10] Seventy-five (91%) children of the typically developing group had no current Axis I diagnosis; current diagnoses in the remaining 7 children included ADHD (n = 3), simple phobia (n = 2), social phobia (n = 1), separation anxiety disorder (n = 1), and enuresis (n = 1). The typically developing group only participated on a single occasion. All subjects gave informed assent with parental informed consent as monitored by a local Institutional Review Board.

Neuropsychological Assessments

At the initial assessment, neuropsychological tests (a) were chosen where deficits had been previously identified in unaffected relatives of schizophrenic probands (although generally the findings had been in adults) and (b) were usable across the 6- to 18-year-old age span. Domains covered included visuospatial, language, response inhibition, emotion perception, and working memory; working memory tasks focused on the ability to retain information during distractor conditions. Differences between the genetically vulnerable and comparison groups were most notable in working memory and response inhibition tasks; thus, only results from working memory and response inhibition tasks were included in this analysis.

Working Memory—Sentence Span. Subjects are presented with sets of incomplete sentences and asked to fill in an appropriate word and then asked to recall the stated words at the end of the trial (eg, "On my two hands, I have ten _____."). The raw scores the children receive reflect their ability to recall the words they selected for the completion of the sentences. The number of incomplete sentences presented in each set increases per set of 3 trials.[14] The ability to maintain information on line, while actively engaged in alternative tasks such as completing a new sentence, has been considered a measure of verbal working memory.[14,15]

Working Memory—Counting Span. Participants are presented with cards consisting of target yellow-colored dots that are exhibited among an array of background blue-colored dots.[16,17] The task requires the individual to count the yellow dots and hold that information on line, until he/she is prompted to report the numbers back to the examiner. The ability to maintain information on line, while actively engaged in alternative tasks such as counting the number of dots on a previously unseen card, has been considered a measure of working memory.[18] The task begins with 2 cards, and the number of cards presented in each set and numbers that must be remembered increase when the child correctly completes a trial. The raw score reflects the number of card series correctly completed.

Inhibition—Stopping Task. Computer administered visual choice measure in which the participant must discriminate between 2 go signals, an X and an O, and inhibit their response when cued with an auditory signal; the auditory cue occurs in 25% of trials.[19] After a standard reaction time is determined, the onset of the auditory signal occurs after onset of the stimulus but with a shorter latency than the individual's reaction time. The latency of the auditory signal is varied until the subject is able to successfully inhibit 50% of responses. This task measures the inhibitory response time, or the time necessary to inhibit a programmed response.

Statistical Analysis

Adjustment for Age. There is a strong normal developmental effect on neuropsychological test performance

throughout childhood. To estimate the appropriate adjustment for age, the 82 typically developing comparison subjects without personal or family history of psychosis, ages 6–16 years, completed the neuropsychological task. For each of the dependent measures, a series of linear, quadratic, and cubic polynomials were fit and results were compared after weighting by age raised to a series of powers (−1, 0, ½, 1, and 2). The "best" weighted polynomial model was selected for each dependent variable using Akaike Information Criterion,[20] a procedure based on decision theory for comparing different models for the same data that penalizes for the number of parameters included to avoid overfitting. Once the preferred weighted polynomial was chosen, age-adjusted *z* scores were computed for each individual for each time point.

Stability of Deficits Over Time. The primary goal of this investigation is to assess whether previously identified deficits increase, decrease, or stay stable over time. A paired samples *t* test was utilized to assess whether the group impairment differs at time 1 vs time 2. Effect sizes (Cohen's d[21]) comparing the genetically vulnerable and typical groups for each time point is an alternative way to address this issue; 95% confidence intervals for effect sizes were determined as suggested by Zou.[22] Correlating the initial visit vs repeat visit *z* scores, for the 25 returning subjects, assessed the stability of individual performance across time.

Results

Table 1 summarizes the age-adjusted *z* scores for all 3 dependent measures. Deficits found in the at-risk group at the initial visit have previously been reported.[11] There is no significant difference between first and second visits age-adjusted scores on any of the 3 variables (paired $t = 0.1–0.4$, $P \geq .69$ for all variables). Within the at-risk group, there is a significant correlation across testing session for stopping task stop reaction ($r = 0.74$, $P < .001$) and counting span ($r = 0.41$, $P = .04$) but not for sentence span ($r = 0.11$, $P = .61$). For all 3 tasks, the effect sizes for comparisons with the typically developing group are similar at each time point, suggesting that the severity of the group impairment is stable across the follow-up period. The growth of individual at-risk subjects across time, as compared with the typical comparison group, is represented in figures 1 (for the stopping task stop reaction) and 2 (for counting span).

Discussion

At the initial visit, the at-risk children and adolescents demonstrated small deficits in stop reaction time, counting span, and sentence span.[11] For the smaller sample size in the subgroup who returned for a second visit, the significance was borderline; however, the effect sizes were

Table 1. Age-Adjusted Z Scores for Children of a Schizophrenic Parent (a Genetically At-Risk Group) at 2 Time Points and for a Typically Developing Group

	Age-Adjusted *z* Scores, Mean ± SD			Effect Size: At-Risk Compared With Typical Group (95% Confidence Interval)		Time 2 to Time 1 Comparison for At-Risk Group			
	Typical Group	At-Risk Group, Time 1	At-Risk Group, Time 2	Time 1	Time 2	*t*	*P*	Correlation	*P*
Stopping task	0.00 ± 0.97, *n* = 48	0.79 ± 2.19, *n* = 19	0.67 ± 1.58, *n* = 25	0.46 (−0.08–1.00)	0.50 (0.02–1.00)	0.4	.69	0.76	<.001
Counting span	0.00 ±0.98, *n* = 82	−0.57 ± 1.14, *n* = 25	−0.42 ± 1.01, *n* = 24	0.53 (0.08–0.99)	0.42 (−0.04–0.89)	0.2	.85	0.41	.04
Sentence span	0.00 ± 0.98, *n* = 82	−0.35 ± 1.20, *n* = 25	−0.31 ± 1.05, *n* = 24	0.32 (−0.013–0.77)	0.31 (−0.15–0.76)	0.1	.93	0.11	.61

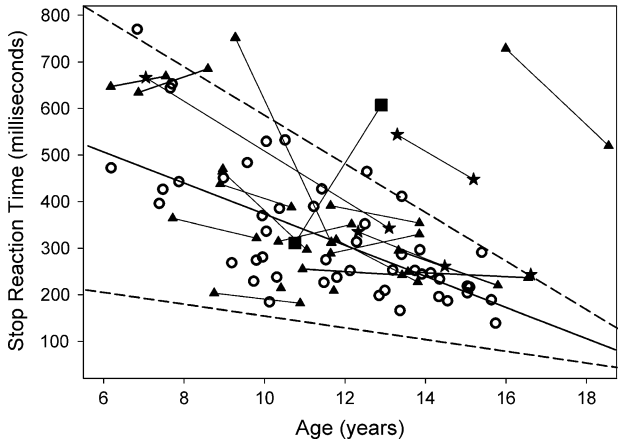

Fig. 1. Stop Reaction Time for Children With a Schizophrenic Parent (Filled Triangles, Stars, and Squares) and a Typically Developing Comparison Group (Open Circles): the Filled Square Represents a Child With a Schizophrenic Parent Who Developed Psychosis Between the First and Second Visits; Filled Stars Represent 4 Children With a Schizophrenic Parent Who Had Already Developed a Schizophrenic Spectrum Illness by Their First Visit. A regression line (thick solid line) ± 2 SEs (dotted lines) represent regression of stop reaction time onto age for the typically developing group. For the children with a schizophrenic parent, age-adjusted stop reaction times correlate between time 1 and time 2 visits, suggesting stability of impairment over time.

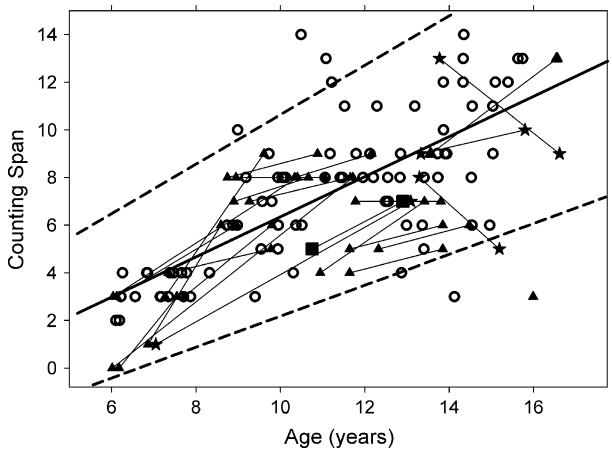

Fig. 2. Counting Span for Children With a Schizophrenic Parent (Filled Triangles, Stars, and Squares) and a Typically Developing Comparison Group (Open Circles): the Filled Square Represents a Child With a Schizophrenic Parent Who Developed Psychosis Between the First and Second Visits; Filled Stars Represent 4 Children With a Schizophrenic Parent Who Had Already Developed a Schizophrenic Spectrum Illness by Their First Visit. A regression line (thick solid line) ± 2 SEs (dotted lines) represent regression of counting span scores onto age for the typically developing group. For the children with a schizophrenic parent, age-adjusted counting span scores correlate between time 1 and time 2 visits, suggesting stability of impairment over time.

similar to those found for the entire group. Notably, for all 3 neuropsychological measures, the effect size was remarkably similar across the 2 visits, with no notable increase or reduction in impairment. In other words, as a group, neuropsychological performance improves because the at-risk children age at the same rate as would be predicted for a typically developing group. For stop reaction time and counting span, this stability of relative performance is present even at the level of the individual with, for the at-risk group, a significant correlation in *z* scores across time. A strong practice effect is unlikely with an over 2-year interval between testing; however, because the typically developing group was only tested on a single occasion, the possibility of a practice effect countering a group-related decrease in function over time cannot be ruled out. Repeat testing of the typically developing group and a larger sample size would be necessary to address this possibility.

Children with psychotic symptoms tended to perform more poorly than average on all the neuropsychological tasks; however, with the exception of one child on the stop reaction task, their performance was within the normal range (figures 1 and 2). Thus, while psychotic children perform poorly, their absolute level of performance may not be sufficiently different from typically developing children to justify neuropsychological testing in this age group as an endophenotype.[23] Only one at-risk child developed a psychotic illness between the first and second visits; his scores are highlighted in figures 1 and 2. The stopping task *z* score for this child worsened by almost 4 SDs between the first and second visits, the largest change of any child in the group. Only 2 other at-risk children showed greater than 1 SD deterioration in performance on the stop reaction task, and only 2 other children showed greater than 1 SD in performance on the counting span task. All 5 children who showed this high level of neuropsychological deterioriation either had psychotic symptoms and/or ADHD. Children with a schizophrenic parent who present with ADHD are at ultrahigh risk for developing a psychotic disorder,[12,24,25] and a deterioration in neuropsychological performance may be an early marker of vulnerability.

There has been significant support for conceptualizing schizophrenia as a neurodevelopmental illness; however, it has been unclear when during development altered brain development occurs. Diagnostic psychotic symptomology often first appears in late teens or early 20s, suggesting that alterations in adolescent brain development contribute to the onset of illness. The current finding that response inhibition deficits are present as young as 6 years of age and are stable throughout childhood suggests that at least some schizophrenia-associated brain dysfunction is fully present by early school age and that etiologic and primary prevention studies may need to focus on preschool or younger ages.[26]

Cognitive deficits in schizophrenia are stable across the course of the illness,[8,9] predict functional impairment,[27,28] and are now considered an appropriate target

for treatment.[29] Individuals with schizophrenia and their first-degree relatives share many cognitive deficits. Because nonpsychotic relatives have limited or absent psychotic symptomology and are not generally treated, these familial deficits are not due to chronic treatment or antipsychotic medications but instead likely have a genetic contribution to etiology. Due to a small sample size, conclusions from this report must be considered preliminary; however, if replicated in larger samples, inhibitory and working memory deficits in nonpsychotic relatives may be stable, even through childhood and adolescence, a period of rapid cognitive development. As etiologic specific treatments are developed for the schizophrenia-associated cognitive deficits, the expansion of those interventions to nonpsychotic individuals with etiologically overlapping cognitive deficits may deserve evaluation.

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