Neurocognitive Functioning in Youth With Pediatric Autoimmune Neuropsychiatric Disorders Associated With Streptococcus

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This study evaluated neurocognitive functioning in 26 youth with Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal infections (PANDAS) and primarily obsessive-compulsive disorder (OCD) symptoms. Marked impairment in visuospatial recall memory (as assessed using the Rey-Osterrieth Complex Figure Test) was observed in spite of average to above-average performance on academic and other neurocognitive measures. Group A beta-hemolytic Streptococcus titer elevations were associated with worse performance on tasks of neurocognitive and executive ability (Stroop Color-Word Interference Test), visuospatial memory, and fine motor speed (finger tapping) as well as elevated obsessive-compulsive symptom severity.

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Obsessive-compulsive disorder (OCD) is a chronic, impairing neuropsychiatric syndrome affecting 1%–2% of young people.[1] A convergence of data from neuropsychological, neuroimaging, and psychopharmacological studies suggest frontostriatal dysfunction in patients with OCD.[2] Individuals with OCD tend to evidence deficits in executive functions (i.e., higher-order cognitive functions, such as response-inhibition, set-shifting, planning, goal-directed behavior, sustained attention, maintenance of cognitive set, working memory, impulse-control, decision-making, and self-regulation) as well as visuospatial abilities and psychomotor functioning.[3,4] Although the etiologies of OCD (and neuropsychological sequelae) are unknown, there is growing support for the concept of immune-related cases of childhood-onset OCD (and OCD-spectrum disorders).

The immunologic phenomenon most putatively linked to OCD-spectrum pathogenesis is Group A beta-hemolytic Streptococcus (GAS).[5] The model for GAS-mediated presentation of OCD involves subcortical (and cortical/cerebellar) inflammation induced by the

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cross-reaction between anti-streptococcal auto-antibodies and basal ganglic antigens.[6] The term Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal infections (PANDAS) has been assigned to the symptoms of these young people with OCD- or tic-spectrum disorders with a temporal relationship between symptom exacerbations and GAS infection, neurological abnormalities during symptomatic periods, and prepubertal, abrupt onset, and/or episodic/saw-tooth course.[7,8] Although many propose that deficits in neuroexecutive and other neurocognitive processes may be considered trait characteristics of obsessive-compulsive spectrum disorders and have the potential to serve as endophenotypic markers,[4,9–12] there has been little research on neurocognitive deficits in youth with PANDAS.[13]

Several studies in youth with OCD suggest deficits in visuospatial functioning, problem-solving, and nonverbal memory,[3,14,15] although others did not find significant differences from healthy control subjects.[16] As an example, patients with OCD have difficulty with a visuospatial memory test, the Rey-Osterrieth Complex Figure Test (ROCF).[15] Other studies have shown that patients with OCD perform worse than do healthy subjects on immediate and delayed recall.[17] Central coherence, impaired information-encoding, and poorer organizational strategies may be largely behind this poorer performance.[18–21] For example, during recall of the ROCF, patients seem to focus on irrelevant details instead of the gestalt of the geometrical structure.[4] In contrast, no deficits were found on a faces-memory task (which requires minimal use of organizational strategies as compared with the ROCF and list-learning tasks).[22] In fact, two recent studies suggest that, in both youth and adults with OCD, executive functioning and visuospatial memory improves with cognitive-behavioral therapy (CBT).[23,24] Flessner et al.[15] suggested that executive performance on the RCFT related to CBT outcome in youth with OCD, and factors such as age and symptom severity may affect this relationship.

Studies of neurocognitive deficits in youth with PANDAS are limited. A recent translational study reported that an animal model of PANDAS had impaired motor coordination and visual-spatial learning/memory.[25] Hirschtritt and colleagues[13] found that youth with PANDAS had greater difficulties with response suppression relative to healthy-control subjects; no group differences were identified on tasks of spatial planning and mental flexibility. Unfortunately, our understanding of neurocognitive functioning among youth with PANDAS is currently very limited. Consequently, the present study aimed to provide an exploratory analysis of neurocognitive functioning in 26 well-characterized young patients with PANDAS.

METHOD

Participants

Twenty-six patients (18 male), ages 4–14 years, with childhood-onset OCD, participated (mean age: 9.9; standard deviation [SD]: 2.1). This study was approved by our institution's Human Subjects Review Board; informed consent was obtained from parents (and assent from each child above the age of 7). Patients were participants in a large, longitudinal study of PANDAS. Each child had been thoroughly assessed by a board-certified child-and-adolescent psychiatrist with expertise in psychoneuroimmunology (TKM) and met putative criteria for PANDAS.[7,26] All patients met diagnostic criteria for OCD, and 19 (73%) met criteria for a comorbid tic disorder as assessed via a diagnostic interview with the same psychiatrist and confirmed using the Kiddie Schedule for Affective Disorders and Schizophrenia, Present and Lifetime (K-SADS–PL).[27] For the present study, each child underwent a neuropsychiatric evaluation (conducted by a Ph.D. clinician), and clinician-rated measures of OCD/tic severity were assessed at the same visit. Sera were also obtained at the same visit as the neuropsychological assessment. Exclusion criteria mirrored that for the overarching study: patients with developmental disabilities, a psychotic disorder, significant medical illness, or non-tic neurological disorder at baseline were excluded.

Neuropsychological Measures

The Rey-Osterrieth Complex Figure Test (ROCF) is a standard test of visuospatial constructional ability, organizational skill, planning, and memory for complex information.[28] The ROCF has three subtests: copy, immediate recall, and delayed recall (administered 30 minutes after the immediate recall). The copy task requires the participant to reproduce a complex figure while in the presence of the stimulus. The recall tasks require the participant to reproduce the same figure from memory. There is also a recognition task, during which the participant is presented with aspects of the figure and is asked to indicate whether they were part

of the design (administered after the delayed-recall condition). Age-corrected T-scores were provided, except in the case of the copy task (where an age-base percentile was utilized). Strong psychometric properties have been published for this measure.[29–31]

The Stroop Color–Word Test's Interference Score[32] is a measure of cognitive flexibility, assessing the ability to shift attention and inhibit the prepotent response. In this task, the patient must inhibit the automatic response (word-reading) and provide the name of the ink color (e.g., saying "red" when the word "blue" is printed in red ink). Scoring controls for the participant's speed at both word-reading and color-naming. Strong test–retest reliability has been demonstrated in previous studies (r=0.90, 0.83, and 0.91 for the word-reading, color-naming, and color–word interference tests).[31] Age- and gender-corrected T-scores are provided.

The Trail-Making Test (TMT)[33] is a two-part, timed, paper-and-pencil task. Part A requires a child to connect, as rapidly as possible, a series of consecutively-numbered circles randomly scattered on a page. Part B involves alternating between numbers in sequence (as in Trails A) and letters in alphabetical order (1, A, 2, B, 3, C, etc.). Trails B probes executive function by requiring the individual to hold two sequences in working memory and alternate between them. Age- and gender-normed T-scores are provided. Documented reliability (reported as coefficients of concordance) is high for both scales (0.98 and 0.67 for Parts A and B, respectively).[31]

The Finger-Tapping Test (FTT) is a measure of fine motor speed. The child is instructed to tap rapidly for 10 seconds, using his or her index finger (alternating between hands on consecutive trials). The average of five trials (within 5 taps of each other) was used, and tapping was recorded on a mechanical tapper.[34] Age-norms were used to calculate z-scores.

The Purdue Pegboard Test is a speeded test of dexterity and hand–eye coordination, requiring the child to place pegs, one at a time, into holes until a time of 30 seconds has elapsed.[35] Study participants alternated between their dominant and nondominant hands, and the examiner left all pins in place until both the dominant and nondominant hands had been tested. The examiner then counted and recorded the number of pins inserted by each hand. Age-based z-scores were calculated and employed in this research.

The Wide Range Achievement Test, 3rd Edition (WRAT–3) an individually-administered test of achievement, was used to screen basic skills of reading, spelling, and arithmetic.[36] The WRAT–3 was administered to provide a more global estimate of functioning (in contrast to the more specific neuroexecutive and cognitive domains assessed on the other measures). Strong internal consistency and alternate-forms reliability (immediate and delayed) have been documented.[36]

Measures of Neuropsychiatric Symptom Severity

The Children's Yale-Brown Obsessive-Compulsive Scale (CY-BOCS) is a clinician-rated, semistructured interview for the rating the severity of obsessive-compulsive disorder.[37] Children and/or the children's guardians are asked to indicate whether the children possess obsessive and compulsive symptoms and to rate the severity of the symptoms. Each of the 10 items is scored on a 5-point scale, from 0 to 4, yielding an Obsession score, 0–20 a Compulsion score, 0–20 and a Total score. 0–40 Reported internal consistency (α=0.87) and intraclass correlations (ICC=0.84) are strong for this measure.[37]

The Yale Global Tic Severity Scale (YGTSS)[38] is a clinician-rated, semistructured interview that begins with a systematic inquiry of tic symptoms in the preceding week. Current motor and phonic tics are then rated separately according to number, frequency, intensity, complexity, and interference on a 6-point ordinal scale. Scores range from 0 to 50, with higher scores suggesting greater tic severity. Strong psychometric properties have been documented for the YGTSS.[38]

Laboratory Measure: Streptococcal Antibodies

The antistreptolysin O (ASO) titer was collected as an assay of streptococcal antibodies. The ASO assay was performed in the University of Florida's Streptococcal Antibody Laboratory. After each visit, the sample was immediately stored at −80°C as duplicates in separate freezers. Assays were performed by an experienced technician blind to all neuropsychiatric results. Known control samples (predetermined as High, Medium, Low) were used to calibrate the assay. Two internal-control sera of known antibody titer were obtained from a reference lab. The Sure-Vue ASO test kit[39] was used. Reagents used, reading, and interpretation of the test have been described.[40] The threshold for classifying an antibody as elevated was set at >200 for the ASO. This threshold has not been age-adjusted, and perhaps results in some false negatives for children in the preschool age range.[41]

TABLE 1. Descriptive Data for Study Measures

Measure/Scale	Score	Mean	Median	SD	Skew	Kurtosis	Range
ROCF Immediate Recall	T	27.2	28	16.1	−0.19	0.08	1–64
ROCF Delay	T	25.8	27.5	15.3	−0.23	−0.17	1–59
ROCF Recognition	T	48.1	46.5	13.4	−1.3	3.3	1–67
Trails A	T	43.2	45	7.0	−0.29	−0.63	1–56
Trails B	T	46.6	46	10.8	0.55	0.44	28–56
Stroop Color–Word Interference	T	49.8	49	9.5	0.42	0.98	25–70
Stroop Color-Naming	T	48.2	47.0	9.9	0.86	0.68	32–71
Stoop Word-Reading	T	50.6	51.0	7.1	0.46	0.90	36–64
Purdue Pegboard (Dominant)	Z	0.3	27.0	0.9	0.20	−0.23	−1.38–1.98
Purdue Pegboard (Non-dominant)	Z	−0.09	−0.18	1.2	0.70	0.18	−2.25–2.35
Tapping (Dominant)	Z	0.9	0.79	1.4	−0.14	−0.38	−1.97–3.54
Tapping (Non-dominant)	Z	0.7	0.8	1.5	0.15	−0.67	−1.77–3.76
Reading	S	107.6	108	13.4	−0.10	0.79	75–138
Spelling	S	105.5	107	15.4	−0.82	0.59	69–134
Math	S	105.4	106	9.9	−0.58	0.46	83–124

T: T-score; Z: Z-score; S: Standard Score; SD: standard deviation; ROCF: Rey Osterrieth Complex Figure.

Data Analysis

For neuropsychological testing, data are reported as age- (or age/gender)-corrected scores. Normative data were obtained from the relevant manuals[29,32,35,36] or from a compendium of published normative data for neuropsychological testing in children.[31] Correlations among study measures are also presented; *t*-tests were used to evaluate group differences (between youth with and without current titer elevations) in clinical and neuropsychological measures. Given the exploratory nature of this study, no Bonferroni or other statistical corrections were employed. Also, because our relatively small sample makes the traditional level of significance an overly stringent criterion, effect sizes were presented (Cohen's δ) to highlight the magnitude of mean differences; δ values ≥0.60 are considered a large effect size.[42]

RESULTS

For neuropsychological measures, means and distributions are presented in Table 1; intercorrelations are presented in Table 2.

Rey-Osterrieth Complex Figure Test (ROCF) The ROCF copy task was administered to assess perceptual organization and visual-spatial memory. Performance on the copy task suggested pervasive impairment, with 84% of participants scoring below the first percentile. Only two participants scored above the 16th percentile (6.5%). Participants were able to use extra time on the ROCF copy task if desired, but showed no improvement in results when extra time was taken.

The ROCF immediate recall task was also indicative of problems for this sample of youth with OCD/PANDAS. Only one participant scored above average. More than 80% scored below 1 SD; 58% scored below 2 SDs; and 19.4% scored below 3 SDs. Performance was similar on the ROCF delayed recall task. Again, only one participant scored above the 50th percentile (T=59), whereas 22.6% had scores more than 3 SDs below the mean. Recognition trials were less suggestive of impairment, with 45% of youth scoring above the 50th percentile (and only 9.7% scoring more than 2 SDs below the mean).

Trails Most youth in this sample scored within 1 SD of the average on Trails A (58.3%). T-scores ranged from 28 to 56. Performance was similar for Trails B, with 52.2% scoring within 1 SD of the mean (range: 25–70).

Stroop On the Stroop Color–Word Interference Task, most youth scored in the average range (80% between T=40 and T=60; range: 33–75); no youth scored more than 2 SDs below the mean, and the distribution approached normal.

Fine-Motor Testing On the Purdue Pegboard task, a roughly normal distribution was obtained. All youth scored within 1 SD of the mean, using the dominant hand (z-scores ranged from –1.4 to 1.98). Variance for the nondominant hand was slightly larger (z-scores ranged from –2.23 to 2.53), but 89.4% of youth scored with 1 SD of the mean. On a timed finger-tapping task, the distribution also appeared normal for the dominant hand (z-scores ranged from –1.97 to 3.54; 84% were

TABLE 2. Correlation Coefficients for Study Measures

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
1. ROCF Immediate Recall	1.00															
2. ROCF Delay	0.93***	1.00														
3. ROCF Recognition	0.15	0.17	1.00													
4. Trails A	−0.18	−0.11	−0.41*	1.00												
5. Trails B	−0.38	−0.45*	−0.46*	0.47*	1.00											
6. Stroop Color–Word	0.33	0.34	0.34	−0.65***	−0.42*	1.00										
7. Pegboard (Dominant)	0.61**	0.58**	0.23	−0.13	−0.09	0.27	1.00									
8. Pegboard (Non-dominant)	0.18	−0.03	−0.08	−0.24	0.11	0.15	0.30	1.00								
9. Tapping (Dominant)	0.24	0.20	0.22	−0.29	−0.05	0.46*	0.38	0.12	1.00							
10. Tapping (Non-Dominant)	0.32	0.23	0.43*	−0.47*	−0.24	0.58**	0.28	0.15	0.87***	1.00						
11. Reading	0.11	0.18	0.29	−0.29	−0.18	0.41*	0.15	0.07	0.16	0.19	1.00					
12. Spelling	0.41*	0.54**	0.15	0.05	−0.17	0.25	0.26	−0.04	0.07	−0.02	0.60**	1.00				
13. Math	0.40	0.47*	0.01	−0.04	−0.34	0.23	0.18	0.18	−0.05	−0.07	0.48*	0.65***	1.00			
14. CY-BOCS Total	−0.22	−0.27	−0.10	−0.12	−0.14	0.37	−0.38	0.19	0.03	−0.03	0.01	−0.22	0.12	1.00		
15. YGTSS Total	0.13	−0.09	0.02	0.14	−0.09	−0.08	−0.09	−0.06	0.13	0.21	−0.17	−0.32	−0.40	−0.17	1.00	
16. ASO Titer	−0.30	−0.33	0.05	0.17	0.11	−0.36	−0.43	−0.18	−0.18	−0.18	−0.27	−0.25	−0.05	0.03	−0.06	1.00

CY-BOCS: Children's Yale-Brown Obsessive-Compulsive Scale; YGTSS: Yale Global Tic Severity Scale; ASO: antistreptolysin O.
*p <0.04; **p <0.01; ***p <0.001.

TABLE 3. Neuropsychiatric Symptom Differences, Based on Titer Status

	Not Elevated (N=12)		Elevated (N=14)				
Measure/Scale	**Mean**	**SD**	**Mean**	**SD**	**t**	**p**	**Cohen's δ**
ROCF Immediate Recall	34.75	12.51	20.79	16.41	2.41	0.02	0.96
ROCF Delay	32.25	14.16	20.21	14.48	2.13	0.04	0.84
ROCF Recognition	48.67	18.37	47.64	10.50	0.18	NS	0.07
Trails A	42.50	6.87	43.92	7.44	−0.49	NS	−0.20
Trails B	45.64	12.72	47.50	9.21	−0.41	NS	−0.17
Stroop Color–Word Interference	54.17	9.12	45.69	8.11	2.46	0.02	0.98
Stroop Color-Naming	49.08	12.39	47.46	7.49	0.4	NS	0.15
Stoop Word-Reading	50.50	8.70	50.77	5.59	−0.09	NS	−0.04
Purdue Pegboard (Dominant)	0.31	0.93	0.10	0.97	0.56	NS	0.22
Purdue Pegboard (Non-dominant)	−0.38	1.63	−0.05	0.90	−0.62	NS	−0.25
Tapping (Dominant)	1.32	1.10	0.48	1.59	1.53	0.14	0.61
Tapping (Non-dominant)	1.22	1.25	0.24	1.60	1.70	0.10	0.68
Reading	111.00	7.22	105.00	16.54	1.12	NS	0.47
Spelling	109.27	12.27	102.57	17.27	1.09	NS	0.45
Math	105.18	11.20	105.64	9.19	−0.11	NS	−0.04
YGTSS Total	17.45	16.27	15.00	14.76	0.36	NS	0.16
CY-BOCS Total	13.18	10.22	19.50	9.45	−1.47	0.16	−0.64
ASO Titer mean	125	21	386	363	−2.70	0.01	−1.02

ROCF: Rey Osterrieth Complex Figure; SD: standard deviation; YGTSS: Yale Global Tic Severity Scale; CY-BOCS: Children's Yale-Brown Obsessive-Compulsive Scale; ASO: antistreptolysin O.

within 1 SD of the mean) and the nondominant hand (z-scores ranged from –1.77 to 3.76; 84% within 1 SD of the mean).

Achievement Testing Youth in this sample generally scored in the average to above-average ranges on tests of reading, spelling, and mathematical abilities. On the reading test, all but one child scored equal-to or above the Standard Score (S) of 89, and 24% scored better than 1 SD above the mean. Sixty-four percent scored above the mean. On the spelling subtest, only four youths scored below SD 0.85 and 28% scored more than 1 SD above the mean. Seventy-six percent scored above the mean on the spelling subtest. Similarly, on the mathematics subtest, two participants scored below S85; 8% scored more than 1 SD above the mean; 72% scored above the mean.

Neuropsychiatric Symptoms Related to ASO Titer Status Youth with current ASO titer elevations scored worse on immediate and delayed visual-spatial memory tests, in contrast to youth without titer elevations. This difference is clinically significant: the youths with elevated titers scored 3 SDs below average, whereas those without concomitant titer elevations at the time of testing had mean visual-spatial memory scores of only 1.5 SDs below average. Recognition memory did not differ between groups. However, youth with ASO elevations also had lower scores on the color–word inhibition task. Each of these group differences were of a large effect size. Patients with elevated titers also had elevated OCD symptom severity and lower speeded dexterity. Raw scores did not differ by group. Data are presented in Table 3.

DISCUSSION

This study presents a preliminary illustration of neuropsychiatric functioning in youth with PANDAS. Notably, young people with PANDAS presented with markedly impaired performance on tasks of visual-constructive and visual-spatial recall memory. The only extant examination of neuroexecutive defects in youth with PANDAS did not find large group differences on tasks of visual-spatial planning and organization.[13] These profound deficits are in the context of no other identified neurocognitive impairments within a sample that exhibited academic achievement scores well above average. This is consistent with previous findings suggesting no difference in intellectual functioning between youth with PANDAS and healthy controls.[13] Also, recognition memory appeared intact.

Of equal interest is the relationship between titer elevation and neurocognitive performance. Each of the youth in this study met putative criteria for PANDAS

and DSM-IV-TR criteria for OCD; each has a documented history of titer elevations. Notably, youth with titer elevations at the time of the neuropsychological assessment have dramatically lower scores on delayed and immediate visual-spatial recall tests as well as on a test of executive control (requiring inhibition and selective attention). Those with elevated titers also scored more poorly on a timed fine-motor test.

Although we did not find statistically significant correlations between OCD symptom severity and neurocognitive tests, OCD symptom severity was significantly higher in youth with elevated titers. Those with elevated titers showed more visuospatial memory, executive, and fine-motor impairments than youth without titer elevations. It is possible that a mediating relationship exists wherein titer elevations affect OCD severity and, consequently, neurocognitive processing; replication in a larger sample may provide the statistical power to make this determination.

There are a number of noteworthy limitations to discuss. First, this is an exploratory study, with a limited sample size; consequently, many of our analyses were underpowered. Second, we were unable to track neuropsychological changes with changes in titer elevations longitudinally (i.e., a within-subjects analysis). Third, our subjects had primary OCD, and, consequently, this report does not evaluate neurocognitive functioning in youth with PANDAS with primary tic presentations (without clinically significant OCD). Notably, with the exception of dominant-hand Purdue Pegboard performance in male subjects, Sukhodolsky and colleagues found that youth with chronic tics did not differ from healthy-controls on tasks of visual-motor integration and response inhibition.[43] Finally, despite a lengthy battery of neurocognitive performance tests and tests of academic achievement, no formal IQ measure or test of verbal memory or fluency was included in our battery.

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