Cognitive, Graphomotor, and Psychosocial Challenges in Pediatric Autoimmune Neuropsychiatric Disorders Associated With Streptococcal Infections (PANDAS)

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Objectives: Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection (PANDAS) is characterized by the sudden onset of obsessive-compulsive disorder (OCD) and other neurobehavioral symptoms following group A streptococcal infection. The cardinal neuropsychiatric symptoms are believed to reflect an aberrant autoimmune or inflammatory response that may selectively disrupt basal ganglia function. The investigators examined whether neuropsychological skills associated with frontostriatal networks (executive functions and motor skills) are affected in patients with PANDAS following resolution of acute symptoms and the degree to which there are persistent social, emotional, and academic difficulties.

Methods: Twenty-seven patients ages 6–14 years (mean age=9.63 years [SD=1.78]; male, N=22) completed neuropsychological testing as part of routine clinical care. Performances on measures of intellectual ability, executive function, motor skills, and academic skills are reported, as well as parent-reported emotional, behavioral, and social skills.

Results: On neuropsychological measures, patients exhibited average intellectual functioning with relative and mild difficulties in skills supporting cognitive efficiency, including attentional regulation, inhibitory control, and processing speed. Dexterity was normal but graphomotor skills were reduced. Core reading, math, and writing skills were within expectations, but reading and math fluency were reduced, and the majority of patients received special education services or accommodations. Parents reported high levels of concern about anxiety, depression, inattention, hyperactivity, and social skills.

Conclusions: These findings indicated relative difficulties with aspects of executive and motor functions. Although evaluations were performed following the resolution of acute symptoms, ongoing and significant academic difficulties and emotional, behavioral, and social concerns were targets for clinical intervention and support.

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Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS) is characterized by the rapid onset of obsessive-compulsive disorder (OCD) in the days to weeks following a streptococcal infection (1). Frequently, additional neuropsychiatric symptoms also emerge, including attentional difficulties, mood disruption, motor or vocal tics (2), and other behavioral changes (e.g., a decline in handwriting, nocturnal enuresis) (3, 4). Symptoms often improve as the acute phase of the illness resolves but may persist without treatment or with recurrent group A streptococcal infections. Preliminary studies using antibiotics (5) and anti-inflammatory therapies (6–8) have shown efficacy in patients with PANDAS, although a mechanistic link between inflammation and neuropsychiatric symptoms in PANDAS has yet to be conclusively demonstrated.

The diagnosis of PANDAS requires careful differentiation from overlapping psychiatric syndromes, particularly childhood-onset OCD, attention deficit hyperactivity disorder (ADHD), and tic disorders (including Tourette's syndrome). PANDAS must also be distinguished from Sydenham's chorea, a poststreptococcal inflammatory syndrome characterized by the abrupt onset of chorea (dance-like movements). Current PANDAS diagnostic criteria require the abrupt onset of OCD or a tic disorder in a pediatric patient (age 3 to onset of puberty) or a relapsing and remitting course of clinical symptoms. The diagnosis also requires a temporal relationship between a streptococcal infection and the onset or exacerbation of symptoms; these exacerbations typically involve increases in OCD or tic symptoms, as well as movement abnormalities and hyperactivity (2).

Multiple convergent lines of evidence suggest that OCD and tic symptoms are related to dysfunction in a series of neuronal networks connecting the basal ganglia, thalamus, and cerebral cortex, termed the cortico-striato-thalamo-cortical

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circuit (9–13). The OCD and tic symptoms of PANDAS, specifically, are hypothesized to result from either an autoimmune or inflammatory disruption of cortico-striato-thalamocortical circuits. Recent studies have shown structural and functional neuroimaging abnormalities in the basal ganglia; antibodies isolated from children with PANDAS, compared with control subjects, selectively recognize a subtype of neuron in the basal ganglia of postmortem human brain (14–18). If PANDAS symptoms reflect selective involvement of these networks, as the autoimmune antibody data suggest, then patients with PANDAS may exhibit a distinct neuropsychological profile of vulnerability within cognitive, affective, or behavioral domains (19–22). Specifically, weaknesses in aspects of executive function related to cognitive efficiency may follow disruption of basal ganglia networks, including inattention, cognitive slowing (slow processing speed), reduced verbal initiation, difficulties with set-shifting, disinhibition, and reduced working memory (22–25). Affective changes may include mood dysregulation, ranging from anhedonia to mania and psychosis (22, 26, 27). Behavioral changes may include motor impairment, including difficulties with fine motor coordination and precision (22, 28).

Neuropsychological profiles of patients with PANDAS have not been extensively studied; accordingly, we present comprehensive findings from a well-characterized cohort of PANDAS patients who completed clinical neuropsychological evaluations. Previous studies of cognitive functioning in patients with PANDAS have found reduced performance on a visual memory test (29), reduced sustained attention and response suppression (30), and reduced processing speed (31). We aimed to extend this research and specifically examined whether skills associated with frontostriatal networks, namely graphomotor skill and executive functions associated with cognitive efficiency, are selectively impaired in a clinical sample of patients with PANDAS. Measures of academic achievement are also reported, including academic fluency and writing, which require the integration of executive function and motor skills. Parent-reported psychosocial functioning is also described, in addition to behavioral and emotional functioning.

METHODS

Participants

A total of 27 patients diagnosed with PANDAS were referred for neurocognitive testing. All participants met full diagnostic criteria for PANDAS (2) as determined by a board-certified child psychiatrist (K.A.W.) with expertise in the diagnosis and management of PANDAS. Participants were referred for clinical neuropsychological evaluations over a 4-year period as part of routine clinical care. All neuropsychological evaluations were either conducted or supervised by a board-certified neuropsychologist (M.K.C.).

This research was conducted as a retrospective review of medical records. All procedures were reviewed and approved by the institutional review board of Massachusetts General Hospital/Harvard Partners.

Neuropsychological Assessment

Evaluations consisted of a clinical interview with a parent or legal guardian, a clinical interview with the patient, review of available medical records, parent rating scales completed at the time of the neuropsychological evaluation, and completion of a battery of norm-referenced and standardized neuropsychological tests. For the parent rating scales and standardized neuropsychological tests, raw scores were converted to z-scores using published age-appropriate normative data. Neuropsychological test data were grouped by cognitive, motor, and academic functioning domains (for further details, see Table S1 in the online supplement). For each patient, a composite z-score was calculated for each domain by averaging z-scores for all administered measures within a given domain. In keeping with standardized assessment procedures, measures were selected on the basis of the availability of age-appropriate normative data, resulting in variability of the number of tests and specific tests included in a composite score. For example, during evaluations, the measure to assess inhibitory control was selected on the basis of the availability of age-appropriate normative data (e.g., NEPSY-II Inhibition for ages 6–7, DKEFS Color-Word Interference Test for children ages ≥8). In this manner, normalized clinical data from measures assessing the same cognitive construct could be combined across the sample.

Intellectual functioning. All patients completed a measure of broad intellectual functioning, either the Wechsler Intelligence Scale for Children, Fourth Edition (WISC-IV; N=2) or Fifth Edition (WISC-V; N=25) (32, 33). The General Ability Index (GAI) was used as the overall measure of intellectual functioning; this factors verbal and nonverbal abilities independently from working memory and processing speed, as the latter measures are areas of interest and may show relative weaknesses in clinical populations that confound estimates of full scale intelligence quotient (FSIQ) (34).

Executive functions. Broadly, executive functions are skills that support goal-directed behavior and novel problem solving. This study included assessment of executive functions linked to subcortical networks involving the frontal lobes and supporting cognitive efficiency, which were the primary interest in this study, and included attentional regulation (inattention), inhibitory control (inhibition), processing speed, cognitive set-shifting (switching), verbal fluency, and working memory (see Table S1 in the online supplement).

Motor functions. Measures of graphomotor precision and dexterity (dominant and nondominant) are presented in Table S1 in the online supplement

Academic functions. To assess academic skills, patients completed subtests of the Wechsler Individual Achievement

Test–Third Edition (35), Test of Oral Word Reading Efficiency (first or second edition) (36, 37), and Gray Oral Reading Test–Fifth Edition (38). Skills were grouped into word decoding, reading fluency, spelling, writing, writing fluency, mathematics, and math fluency. (For further details, see Table S1 in the online supplement.)

Parent Behavioral Ratings

Behavioral Assessment Scale for Children (BASC). To assess emotional and behavioral functioning, parents (N=27) completed the BASC (second or third edition). Questions on the BASC generate scales to assess internalizing problems, externalizing problems, school problems, and adaptive skills. Clinical scales of interest were defined on the basis of symptoms associated with diagnostic criteria for PANDAS, including anxiety, depression, inattention, hyperactivity, and ability to execute activities of daily living (39, 40).

Behavior Rating Inventory of Executive Functions (BRIEF). Parents completed the BRIEF (N=27), a standardized questionnaire designed to assess a child's ability to apply aspects of executive function in daily life. Subscales are grouped into those related to behavioral regulation (inhibition, shifting, and emotional control) and metacognition (initiation, working memory, planning and organization, organization of materials, and monitoring) (41). The Behavioral Regulation Index and Metacognition Index were analyzed.

Social Responsiveness Scale–Second Edition (SRS-2). To assess social functioning, parents completed the SRS-2 (N=23). The SRS-2 is a standardized questionnaire designed to assess social communication difficulties that are common in autism spectrum disorder (42). Subscales include social awareness, social cognition, social communication, social motivation, and restricted interests and repetitive behaviors. The variable of interest was the *DSM-5* compatible composite score assessing social communication and interaction that is calculated from all scales except for restricted interests and repetitive behaviors.

Statistical Analyses

Overall intellectual functioning. All patients completed the WISC. Repeated measures analysis of variance was used to determine whether the overall WISC index scores were significantly different from one another. A one-sample t test was conducted to determine whether the PANDAS sample's mean GAI was lower than the WISC normative sample's mean GAI (z=0). Bonferroni correction was used to correct for multiple comparisons (i.e., p value 0.05/number of subscales for each measure).

Neuropsychological and academic domains. To examine discrepancies from aptitude-based expectations, one-sample t tests were conducted to determine whether executive functions, motor functions, and academic skills were lower than expected. For cognitive skills (executive functions and academic skills), comparisons were made to the PANDAS sample's mean GAI. Motor skills were compared with the normative sample's mean (z=0). Bonferroni corrections were applied to correct for multiple comparisons (i.e., p value 0.05/number of variables in each of the three test domains).

Parent and child rating measures. One-sample t tests were conducted to determine whether parent-reported emotional, behavioral, and social functioning were greater than the normative sample's mean (z=0). Bonferroni correction was used to correct for multiple comparisons (i.e., p value 0.05/number of subscales for each measure).

RESULTS

Demographic Characteristics

Data from 27 pediatric patients (ages 6–14, mean=9.63 years [SD=1.78]; grades 1–9, mean=4.07 [SD=1.84]; 22 males; 25 right-handed; all native English speakers) were included in the analysis.

Neuropsychiatric Symptoms and Services

Consistent with diagnostic criteria for PANDAS, all patients (N=27) had a history of clinical OCD symptoms. Fifty-six percent (N=15) had active OCD symptoms at the time of the neuropsychological evaluation, with the average time between reported symptom onset and the neuropsychological evaluation being approximately 2 years (mean=27 months, range=8–72 months, [SD=18.7]). Current and past OCD symptoms, as well as other neuropsychiatric symptoms documented in the medical record, are detailed in Table 1.

Psychiatric treatment history and current medications are summarized in Table 1. The majority of patients (N=18, 67%) were on antibiotic treatment at the time of neuropsychological assessment. A majority (N=16, 59%) were taking prescription psychiatric medications, mostly selective serotonin reuptake inhibitors or alpha-two agonists (N=10, 37%). A majority (N=15, 56%) were engaged in psychotherapy (Table 1).

In addition to OCD symptoms, frequent comorbidities (past or current) included anxiety (85%), mood dysregulation (81%), inattention (78%), tics (70%), sleep difficulties (74%), and sensory sensitivities (67%). Some patients had a history of severe psychiatric symptoms; seven patients (26%) had a history of suicidal ideation, two patients had a history of psychosis (7%), and three patients (11%) had prior inpatient psychiatric hospitalizations (Table 1). None of the patients had an autism spectrum disorder diagnosis.

Parent-Reported Psychosocial Functioning

Compared with normative data, on standardized questionnaires, parents indicated significant anxiety ($p<0.001$) and depression ($p<0.001$). They also reported significant inattention ($p<0.001$), hyperactivity ($p<0.001$), and difficulties with applying aspects of executive function to regulate

TABLE 1. Neuropsychiatric symptoms and treatment for a sample of children with PANDAS (N=27)[a]

Symptom	N	%
OCD symptoms	27	100
Current OCD symptoms	15	56
Sanitary/germ concerns	9	33
Food/eating concerns	4	15
Bedtime rituals	3	11
Compulsive behaviors	14	52
Tics	19	70
Sleep issues	20	74
Anxiety symptoms	23	85
Specific phobias	10	43
Separation anxiety	13	43
Generalized worrying	10	37
Mood symptoms	22	81
Irritability	8	30
Explosive episodes	12	44
Suicidal ideation	7	26
Past psychotic symptoms	2	7
Social concerns	11	41
Inattention	21	78
Hyperactivity/impulsivity	13	48
New-onset nocturnal enuresis	5	19
Sensory sensitivities	18	67
Current psychiatric medications	16	59
Selective serotonin reuptake inhibitors	12	44
Other antidepressants	1	4
Antipsychotics	1	4
Benzodiazepines	1	4
Alpha-2 agonists	10	37
Stimulants	4	15
Anticonvulsants	1	4
Current antibiotic treatment	18	67
Current steroid/anti-inflammatory treatment	6	22
Other medications (e.g., antihistamines)	11	41
Current psychotherapy	15	56
Past inpatient hospitalization	3	11

[a] OCD=obsessive-compulsive disorder, PANDAS=pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection.

behavior ($p<0.001$) and solve problems ($p<0.001$). They also indicated significant social communication difficulties ($p=0.004$). Altogether, adaptive skills were rated as below age-based expectations ($p=0.006$) (Table 2).

TABLE 2. Parent-reported symptoms on standardized questionnaires

Symptom	Mean[a]	SD	t[b]	p
Behavioral regulation	0.96	1.12	4.46	0.00
Metacognition	0.98	1.25	4.09	0.00
Inattention	0.98	0.9	5.43	0.00
Hyperactivity	1.13	1.16	4.76	0.00
Anxiety	0.94	1.07	4.41	0.00
Depression	0.75	0.84	4.58	0.00
Social communication	0.63	0.94	3.19	0.004
Activities of daily living	−0.74	1.21	−3.04	0.006

[a] Mean scores are z-scores.
[b] Comparison relative to normative population mean (z=0).

Parent-Report Developmental History

Notable aspects of parent-reported developmental history (e.g., pre- or perinatal complications, developmental delays) are characterized in Table 3. There were relatively high rates of early developmental concerns that predated the onset of PANDAS symptoms: 33% (N=9) had a history of prematurity, and 30% (N=8) received formal early intervention services for developmental delays. Including these patients, there were concerns about early developmental delays in either language or motor skills in 41% (N=11) of the sample (Table 3). Altogether, 67% (N=18) had a parent-reported history of prematurity, early intervention services, or developmental delays.

Neuropsychological Functioning

Intellectual functioning. WISC index scores (Verbal Comprehension Index [VCI]; Perceptual Reasoning Index [PRI]; Working Memory Index; and Processing Speed Index) were significantly different from each other ($F=4.39$, df=3, 24, $p=0.013$), validating use of the GAI as a better indicator of overall intellectual functioning than FSIQ. Higher GAI mean score compared with the WISC normative population mean fell short of statistical significance (mean=0.34 [SD=0.89], $p=0.06$). Verbal (VCI) and nonverbal (PRI) abilities were evenly developed and slightly higher than the WISC's normative mean (Table 4).

Executive functions. Relative to the PANDAS sample's GAI, attention ($t=-5.02$, df=21, $p<0.001$), inhibition ($t=-5.75$, df=26, $p<0.001$), and processing speed ($t=-4.17$, df=26, $p<0.001$) were areas of significant difficulty (corrected $p<0.01$). Switching as an area of concern fell short of statistical significance ($t=-2.27$, df=25, $p=0.032$). Working memory ($t=-1.5$, df=26, $p=0.15$) and verbal fluency ($t=0.92$, df=26, $p=0.37$) were within aptitude-based expectations (Table 4).

Motor skills. Relative to the normative mean, patients had significant difficulty with graphomotor skill ($t=-6.99$, df=26, $p<0.001$). Dexterity was within normal limits ($t=1.97$, df=24, $p=0.06$) (Table 4).

Developmental history. Supplementary post hoc t tests compared patients who had a history of either prematurity, developmental delay, or early intervention services (N=18) to those without a history of developmental complications (N=9). There were no significant differences between groups in overall intellectual functioning (WISC-V GAI), executive functions (attention, inhibition, processing speed, switching, working memory, and verbal fluency), or motor skills (graphomotor skill, dexterity) (all p values >0.07).

Academic Functioning

At the time of the neuropsychological evaluation, nearly all patients (N=25, 93%) reported some academic concerns.

TABLE 3. Parent-reported developmental and academic concerns

Concern	N	%
Developmental delay	11	41
Language	6	22
Gross motor/coordination	3	11
Fine motor/coordination	4	15
Received early intervention services (<3 years old)	8	30
Prematurity	9	33
Any reported pre- or perinatal complications	10	37
Academic difficulties	25	93
Reading difficulties	15	56
Writing difficulties	18	67
Math difficulties	15	56
Writing concerns	19	70
Receiving services and accommodations as part of an individualized education program	9	33
Receiving accommodations as part of a 504 Plan	8	30

Seventeen patients (63%) were receiving special education services or accommodations through their local public school, nine (33%) were receiving services and accommodations as part of an individualized education program, and eight (30%) were receiving accommodations as part of a 504 Plan. In the clinical interview, the majority of parents endorsed significant problems with handwriting (N=19, 70%) and writing (N=18, 67%). Approximately half of parents endorsed significant difficulties with reading (N=15, 56%) and math (N=15, 56%) (Table 3).

On formal testing, relative to the patient sample's GAI (corrected $p<0.006$), reading fluency ($t=-3.94$, df=21, $p=0.001$) and math fluency ($t=-4.68$, df=14, $p<0.001$) were below aptitude-based expectations. All other academic skills were within aptitude-based expectations, including single word decoding, spelling, math, writing skills, and writing fluency (Table 4).

TABLE 4. Performance on measures of intellectual, executive, motor, and academic abilities in children with pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection

Variable	Mean[a]	SD	t	p
Overall intellectual functioning[b]				
Full intelligence quotient	0.23	0.84	1.31	0.20
General ability	0.34	0.89	2.00	0.06
Verbal comprehension	0.46	0.87	2.76	0.01
Perceptual reasoning	0.32	0.79	2.11	0.04
Working memory	0.06	0.98	0.31	0.76
Processing speed	−0.38	0.89	−2.19	0.04
Executive functions[c]				
Inattention	−0.61	0.88	−5.02	0.00
Inhibition	−0.26	0.54	−5.75	0.00
Processing speed	−0.38	0.89	−4.17	0.00
Switching	0.004	0.75	−2.27	0.03
Verbal fluency	0.48	0.78	0.92	0.37
Working memory	0.06	0.9	−1.5	0.15
Motor functions[b]				
Graphomotor precision	−0.96	0.71	−6.99	0.00
Dexterity	0.28	0.72	1.97	0.06
Academic skills[c]				
Word decoding	0.1	0.95	−1.30	0.20
Reading fluency	−0.42	0.91	−3.94	0.001
Spelling	−0.1	1.08	−2.05	0.05
Writing	0.17	0.86	−0.98	0.05
Writing fluency	0.18	0.9	−0.86	0.40
Math	0.21	1.15	−0.60	0.55
Math fluency	−0.39	0.61	−4.68	0.00

[a] Mean scores are z scores.
[b] Comparison relative to normative population mean (z=0).
[c] Comparison relative to patient sample's General Ability Index (z=0.34).

DISCUSSION

We reported the clinical characteristics and neuropsychological profiles in a clinical sample of pediatric patients diagnosed with PANDAS. To date and to our knowledge, this is the most comprehensive analysis of neuropsychological performance in a cohort of patients with PANDAS. Overall intellectual functioning fell in the average range (WISC-V GAI: z=0.34, SS=105, 63rd percentile). Relative to their intellectual aptitude, PANDAS patients exhibited weaknesses in cognitive and motor skills. Specifically, patients with PANDAS had greater difficulty sustaining attention, inhibiting responses to stimuli, and quickly integrating and acting upon new information (i.e., exhibited slower processing speed). These findings are consistent with prior studies (30, 31). Parents also endorsed significant inattention and hyperactivity, as well as difficulties applying aspects of executive functions to solve problems (metacognition) and regulate behavior; however, relatively few patients were treated with stimulant medication (N=4, 15%). The degree of difficulty on formal testing was relatively mild; significant scores on measures of cognitive functioning and parent-reported challenges generally fell within one standard deviation of the normative data mean, which is similar to the degree of difficulty reported previously (29). From a diagnostic perspective, the nature of these difficulties overlaps with what is typically associated with ADHD, which is perhaps not surprising given high comorbidity between ADHD and pediatric-onset OCD (43).

Regarding motor skills, nearly all patients (N=25, 93%) were right-handed and dexterity was within age-based expectations bilaterally. However, 70% (N=19) of parents reported writing difficulties in their children, consistent with prior findings that handwriting difficulties are commonly reported in patients with PANDAS (3). On formal testing, patients had greater difficulty than the age-matched normative sample on a graphomotor precision measure requiring them to draw increasingly complex geometric figures (Beery-Buktenica Visual-Motor Integration–Sixth Edition). Lewin et al. (29) also found that patients with

PANDAS had difficulty copying a complex figure despite age-appropriate dexterity. Of note, there were also reported difficulties in freely recalling the same figure after a delay, leading to the conclusion that nonverbal memory may be compromised in patients with PANDAS. Given our finding that verbal and nonverbal intellectual abilities are evenly developed, we suggest an alternative explanation of these findings. Specifically, reduced graphomotor control and difficulties with attentional regulation may be core clinical features of PANDAS; combined, they contribute to reduced initial learning of drawn or copied information, which would also manifest as lower delayed recall scores.

Academic difficulties were frequently reported by parents. Nearly all patients (93%) had some academic concerns, and more than half of the sample (63%) was receiving special education services or accommodations (individualized education program or 504 Plan) at the time of the neuropsychological evaluation. Although we did not always have access to school records to confirm when special education services were initiated, given that some patients received early intervention services, it is likely that some patients also received special education services prior to the onset of their neuropsychiatric symptoms. Writing was identified as an area of particular difficulty; 67% of parents reported writing difficulties. This perhaps reflects written expression's combined demands on graphomotor control and executive functions (e.g., the retrieval and organization of ideas). Performances on formal measures of written expression were within normal limits, but standard scoring did not allow for assessment of the different aspects of writing (e.g., grammar, organization of ideas), and patients had strong verbal skills.

Parents also reported math and reading difficulties in approximately half of the sample (56% each). Yet on formal academic achievement testing, core decoding (reading), spelling, and arithmetic skills were within normal limits, which is consistent with previous findings (29). However, scores on measures of reading and math fluency were significantly below aptitude-based expectations, although still within one standard deviation of the normative mean. In the absence of primary difficulties with reading and math, weaker academic fluency may reflect the functional impact of slower processing speed and difficulties with attentional regulation. Although rates of academic difficulties may be higher in this clinical sample due to selection bias (i.e., patients with academic difficulties may be more likely to be referred for neuropsychological evaluation), the current results suggest that weaknesses in executive functions and motor skills may interfere with academic functioning, such that it should be assessed as part of routine clinical care in children diagnosed with PANDAS.

Finally, there were significant and chronic emotional and social concerns, even though only half (56%) of the sample were reportedly exhibiting OCD symptoms at the time of evaluation and evaluations were, on average, typically completed approximately 2 years after initial symptom onset. On standardized questionnaires, parents endorsed heightened symptoms of anxiety and depression, as well as difficulties with social communication. Social communication concerns were relatively mild, as no patients were diagnosed with autism spectrum disorder, which also suggests that these may be secondary to psychiatric symptoms. On the basis of parent report, generalized worries (37%), separation anxiety (43%), and explosive episodes (44%) were the most common ongoing concerns. Although difficulties were reportedly mild at the time of neuropsychological testing (scores on standardized questionnaires were largely within one standard deviation of the normative mean), higher risk of severe emotional difficulties has been previously reported in PANDAS patients (44). Indeed, in the current sample, 26% had experienced past suicidal ideation, 7% had experienced past psychotic symptoms, and 11% had a prior psychiatric hospitalization. Additionally, at the time of evaluation, approximately half (56%) were taking psychiatric medication or engaged in psychotherapy (56%). More than half (67%) were being treated with antibiotic medication. These data underscore the importance of ongoing psychiatric services as a component of treatment for PANDAS, even with the relapsing and remitting course (45).

These findings raise multiple questions for future research, including the degree to which neuropsychological profiles correlate with biomarkers of immune dysregulation and neuropsychiatric symptom severity. Given that these were clinical neuropsychological evaluations, laboratory data were not obtained simultaneously with neuropsychological evaluation. It is clear that prospective, longitudinal studies of PANDAS patients documenting cognitive, motor, and psychiatric function in relation to concurrent infections are needed. Lewin et al. (29) found that PANDAS children with elevated strep (antistreptolysin O) titers had greater difficulty with graphomotor function, inhibitory control, and dexterity, as well as greater OCD symptoms, suggesting that these weaknesses may be exacerbated during relapses. Our results also suggest that it will be important for future studies to carefully characterize developmental histories, including psychiatric and learning histories, prior to the first PANDAS episode. On the basis of parent report, approximately one-third of patients had a history of prematurity or perinatal complications, and 40% reported mild developmental delays, perinatal complications, and developmental delays. These findings suggest that there may be a measure of neurobiological vulnerability that increases susceptibility to PANDAS and also raise the question about whether weaknesses in neuropsychological skills existed prior to the onset of PANDAS symptoms. Serial monitoring of neuropsychological functioning in PANDAS patients over the course of development will also be important in determining the degree to which fluctuations in markers of immune dysfunction and neuropsychiatric symptoms are associated with changes in cognitive and motor skills. Such studies will allow tracking of symptom severity over time to determine whether symptom severity at diagnosis or

during the worst episode correlates with cognitive or motor difficulties.

Finally, additional research is needed to determine the variability, if any, in neuropsychological profiles of patients with PANDAS compared with other pediatric-onset disorders associated with frontostriatal dysfunction, specifically ADHD, Tourette's syndrome, and OCD (21, 30). Patients in the present study had high rates of clinical symptoms characteristic of these disorders, including OCD symptoms, inattention, hyperactivity, and tics (70%), which is consistent with prior studies of PANDAS patients (46). The neuropsychological weaknesses identified in the present study also highly overlap with those reported in these populations (11, 21, 47–49), suggesting that additional biomarkers in combination with neuropsychological performance may be useful in differentiating PANDAS from these related conditions. However, our study demonstrates that neuropsychological assessment is an important step in fully characterizing the complexity of PANDAS patients' cognitive, academic, and emotional needs, and these findings underscore the importance of neuropsychological evaluation in the care of children with PANDAS.

This study provides a comprehensive perspective on neuropsychological functioning within a clinical sample of patients with PANDAS. On neuropsychological measures, patients exhibited average intellectual functioning with relative and mild weaknesses in attentional regulation, aspects of executive function, and graphomotor skill. Likely reflecting the cumulative effect of these weaknesses, performances on measures of academic fluency were also weak. Parents reported high levels of concern about anxiety, depression, inattention, hyperactivity, and social skills, even well beyond initial symptom onset, as well as the need for special education supports. These findings open multiple avenues for future research and highlight the need for ongoing psychiatric services and academic supports in PANDAS patients.

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