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White matter abnormalities and neurocognitive correlates in children and adolescents with myotonic dystrophy type 1: A diffusion tensor imaging study

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Abstract

Diffusion Tensor Imaging was used to evaluate cerebral white matter in eight patients (ages 10–17) with myotonic dystrophy type 1 (3 congenital-onset, 5 juvenile-onset) compared to eight controls matched for age and sex. Four regions of interest were examined: inferior frontal, superior frontal, supracallosal, and occipital. The myotonic dystrophy group showed white matter abnormalities compared to controls in all regions. All indices of white matter integrity were abnormal: fractional anisotropy, mean diffusivity, axial diffusivity, and radial diffusivity. With no evidence of regional variation, correlations between whole cerebrum white matter fractional anisotropy and neurocognitive functioning were examined in the patients. Strong correlations were observed between whole cerebrum fractional anisotropy and full-scale intelligence and a measure of executive functioning. Results indicate that significant white matter abnormality is characteristic of young patients with myotonic dystrophy type 1 and that the white matter abnormality seen with neuroimaging has implications for cognitive functioning.

1. Introduction

Myotonic dystrophy type 1 (DM1), an autosomal dominant inherited neuromuscular condition, is the most common form of muscular dystrophy with an estimated incidence of approximately 1 in 8000 in the United States. DM1 is the result of mutations on Chromosome 19q13.3, specifically the result of trinucleotide repeat expansion in the 3'-untranslated region of the dystrophin myotonic protein kinase gene (*DMPK*). The disease is progressive and multi-systemic, frequently involving ocular, gonadal, cardiac, and endocrine abnormalities in addition to muscular abnormalities [1–4]. Central nervous system (CNS) involvement is an important clinical component of the disease [5]. CNS effects have been demonstrated in studies examining cognitive function and also in neuroimaging studies [5–9].

Early-onset DM1, which can come to medical attention either at birth or during childhood, is associated with more severe cognitive impairment than the classic adult-onset form of DM1. Congenital-onset DM1, which often occurs with CTG expansions >1000 and presents

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prenatally or at birth, is the most severe presentation and is associated with a very high rate of mental retardation, perhaps between 50% and 90% [5,7,10,11]. Juvenile-onset DM1 is less severe and does not result in mental retardation, but lower than average intelligence quotient (IQ) has been reported [12]. There is evidence that, when individuals with the juvenile-onset form of DM1 reach adulthood, deterioration in frontal-executive functioning can occur, followed by deterioration in memory abilities later in life [11]. By adulthood, deterioration is evident on measures of verbal memory, visual memory, naming, and verbal fluency [13]. Numerous cognitive deficits have been reported in adult-onset DM1 including visual-spatial abnormalities, attention deficits, and impaired executive functioning [8,11,14–19].

The most common brain changes seen in magnetic resonance imaging (MRI) studies of both early-onset and adult-onset DM1 have been ventricular enlargement, cortical atrophy, and white matter hyperintensities [8,14,20–24]. Previous studies have illustrated a very wide range in severity of brain involvement in this disease and some studies, but not all, have shown associations between imaging abnormalities and cognitive function [14,21,25].

In patients with DM1, white matter abnormalities are most commonly seen in subcortical [14] and periventricular [9,26] regions (especially posterior superior trigone) as well as occasionally in other regions including temporal white matter [10,27,28]. The abnormalities seen on MRI have been found to correspond to significant neuropathological changes at autopsy including “severe loss and disordered arrangement of myelin sheaths and axons” [29]. However, some have suggested that neuropathological studies may have underestimated the extent of white matter disruption in myotonic dystrophy [27] and that even ‘normal-appearing white matter’ is disturbed. For example, Naka et al. [30] showed abnormalities in normal-appearing white matter using magnetization transfer imaging (MTI) and DiCostanzo et al. [31] demonstrated widespread white matter disturbance using T2-relaxometry in DM1. Thus far, there has not been a clear convergence of neuropathological findings and neuroimaging findings in DM1.

The nature of the white matter abnormalities in DM1 seen on MRI and their role in the neurocognitive deficits has been only minimally described. To date, there have been few diffusion tensor imaging (DTI) studies of white matter in myotonic dystrophy. Fukuda et al. [32] reported lower fractional anisotropy (FA) in patients with myotonic dystrophy compared to healthy controls. This difference was seen in both normal-appearing white matter and in areas of ‘lesion’ as identified by regions of white matter hyperintensity. Ota et al. [33] used DTI tractography to compare corpus callosum integrity in patients with DM1 to controls and reported significantly lower FA for the patients in multiple regions of the callosum. No correlations between FA and CTG expansion in blood, disease duration, or age at disease onset were found.

The goal of the current study was to utilize DTI to characterize white matter status at the microstructural level in early-onset DM1 and to investigate relationships between white matter abnormalities and cognitive deficits in a group of young patients.

2. Patients and Methods

Consent

The informed consent process included a discussion of the study with the patient and a parent, a consent form signed by the parent, and an assent form signed by the patient. All procedures were reviewed and approved by a University institutional review board.

Subjects

Eight children (4 male, 4 female) with congenital-onset (n=3) or juvenile-onset (n=5) myotonic dystrophy type 1 participated in the study. Subject characteristics are listed in Table 1. Patients were recruited from a University-based myotonic dystrophy clinic. Diagnoses were established by polymerase chain reaction (PCR) and southern blot. The mean age of the patients was 13.75 with a range of 10–17. Patients with DM1 were age and gender-matched with 8 healthy control participants (mean age=13.375), who were recruited from the community.

Neuropsychological Assessment

Subjects completed the following neuropsychological measures: the Wechsler Intelligence Scale for Children (3rd or 4th ed.) [34,35] or the Wechsler Adult Intelligence Scale (3rd ed.) [36], the Wisconsin Card Sorting Test (WCST) [37], and the California Verbal Learning Test (CVLT-II or CVLT-C) [38,39]. Participants who were age 16 or younger were administered either the 3rd and 4th editions of the Wechsler Intelligence Scale for Children (there was a change in the clinical research protocol midway through the study) while 17 year-olds were administered the Wechsler Adult Intelligence Scale. In addition, the Behavior Rating Inventory of Executive Functioning (BRIEF) [40] was administered to the patients' primary caregivers to assess the behavioral expressions of executive function deficits. All neuropsychological instruments were administered by a trained research assistant (E.E.W.) under the supervision of a licensed pediatric neuropsychologist (J.R.W.).

MRI acquisition and processing—Subjects were scanned using a Siemens 3T Trio MRI scanner with an 8-channel parallel array head coil. The scan sequences were as follows:

1. T1-weighted: the images were acquired using a 3D magnetization prepared rapid acquisition gradient (MPRAGE) sequence. Acquisition parameters were: TR=2530ms, TE=3.65ms, TI=1100ms, 224 slices, 1×1×1mm voxel, flip angle=7 degrees, FOV=256×176mm, generalized auto-calibrating partially parallel acquisition (GRAPPA) with acceleration factor=2; 5 minutes.
2. Proton density (PD) -weighted: the images were acquired using a hyper-echo turbo spin echo (TSE) sequence. Acquisition parameters were: TR=8550ms, TE=14ms, 80 slices, 1×1×2mm voxel, flip angle=120 degrees, field of view (FOV)=256mm; 6 minutes.
3. Diffusion tensor imaging (DTI): the 30-direction diffusion-weighted acquisition was positioned to cover the cerebrum and as much of the cerebellum as possible. Acquisition parameters for the dual spin echo, single shot, echo planar, diffusion weighted sequence were: TR=8500 ms, TE=90 ms, 64 slices, voxel size=2×2×2 mm, FOV=256 mm², 1 average, GRAPPA with acceleration factor=2, b=1000 s/mm². Thirty-six volumes each were collected to compute the tensor: 6 images with b=0 s/mm² and 30 images with diffusion gradients applied in non-collinear directions; 6 minutes.
4. Field map: the field map was used to correct the DTI data for geometric distortion. Positioned to match the DTI acquisition. The acquisition parameters were: TR=700ms, TE=4.62 ms /7.08 ms, 64 slices, voxel size=2×2×2 mm FOV=256 mm²; 3 minutes.

Post-processing—Image data was processed using software from the FMRIB Software Library (<http://www.fmrib.ox.ac.uk/>). The brain was extracted from the T1 and PD acquisitions using the brain extraction tool (BET). The PD brain was aligned to the T1 brain

using FMRIB's linear image registration tool (FLIRT), allowing for translations and rotations but no scaling or shear (6 degrees of freedom (DoF) fit). Dual channel segmentation was performed on T1 and aligned PD brains using FMRIB's automated segmentation tool (FAST), producing four tissue classes (cerebrospinal fluid, white, gray, and blood). The T1 brain was registered to the Montreal Neurological Institute (MNI) template brain using FLIRT (12 DoF). A cerebrum mask, which consisted of the whole brain excluding the cerebellum and brain stem, was generated for each T1 image by transforming the template mask created on the MNI brain onto the T1 brain. The DTI data were corrected for eddy current distortion, field maps were used to correct the resulting data for geometric distortions caused by susceptibility induced magnetic field inhomogeneity, and the diffusion tensor was then computed using FMRIB's Diffusion toolbox (FDT). Four scalar measures were derived from the tensor: Fractional Anisotropy (the fraction of the magnitude of the tensor that is due to anisotropic water diffusion [41]); Mean Diffusivity (the mean of the three eigenvalues); Axial Diffusivity (the first eigenvalue); and Radial Diffusivity (the mean of the second and third eigenvalues).

Regions of interest definition—Semi-automated procedures were used to define regions of interest (ROIs) for analysis. A trained operator identified four slices on the MNI aligned T1 image from each subject: the axial slice containing the anterior and posterior commissure (AC-PC), the coronal slice just anterior to the mid-sagittal point of the genu of the corpus callosum, the coronal slice just posterior to the mid-sagittal point of the splenium of the corpus callosum, and the axial slice just superior to the corpus callosum at the longitudinal fissure. Based on these delineations, masks were defined for four regions of interest (ROIs): 1. the *inferior frontal* mask was anterior to the genu and inferior to and including the AC-PC plane (Figure 1); 2. the *superior frontal* mask was anterior to the genu and superior to the AC-PC plane (Figure 1); 3. the *occipital* mask was posterior to the splenium, superior to the AC-PC plane, and inferior to the axial slice just superior to the corpus callosum and; 4. the *supracallosal* mask was superior to the corpus callosum (Figure 2). The ROI masks were transformed from the MNI image to the dewarped DTI images, and then convolved with the white matter mask to yield the ROI specific the white matter mask. Mean fractional anisotropy, mean diffusivity, axial diffusivity, and radial diffusivity values were computed for the white matter within each of the four ROIs.

3. Results

The groups did not differ in age, $F(1, 15) = 1.42, p = .712$. Table 2 contains results from analyses of variance (ANOVAs) comparing groups on several measures of neurocognitive performance. As expected, patients with DM1 performed significantly below controls on standardized IQ measures (Wechsler Intelligence Scale for Children – Fourth Edition or Wechsler Adult Intelligence Scale – Third Edition). Full-scale IQ and all of the index scores were lower for patients with DM1, most notably the Processing Speed Index. Group differences were not significant for measures of verbal learning (California Verbal Learning Test – Children's Edition or 2nd Edition) or executive functioning (Wisconsin Card Sorting Test). However, a parent-report instrument, the Behavior Rating Inventory of Executive Functioning or BRIEF Parent-Report [40], indicated significant “real-world” executive functioning deficits in those with DM1 compared to controls.

For each of the ROIs, a separate multiple analysis of variance (MANOVA) tested for group differences in fractional anisotropy, mean diffusivity, axial diffusivity, and radial diffusivity. A significant group difference was seen in the *inferior frontal* ROI [Wilks' lambda = .136, $F(4,11) = 17.52, p = .0001$]; Univariate tests showed highly significant differences on all white matter indices (Table 3). Similarly, groups were significantly different in the *superior frontal* ROI [Wilks' lambda = .188, $F(4,11) = 11.86, p = .0006$]; Univariate tests showed

highly significant differences on all four indices (Table 4). Again, groups were significantly different in the **supracallosal** ROI [Wilks' $\lambda = .186$, $F(4,11) = 12.06$, $p = .0005$; All four indices differed significantly between the groups (Table 5). Lastly, the groups differed significantly in the occipital ROI [Wilks' $\lambda = .236$, $F(4,11) = 8.92$, $p = .0018$]; All four indices showed significant group differences between the groups (Table 6). In summary, consistent evidence of white matter abnormalities were seen in all four ROIs as reflected by lower fractional anisotropy, higher mean diffusivity, higher axial diffusivity, and higher radial diffusivity in the DM1 group compared to controls.

The relationship between white matter integrity and cognitive status was examined with a set of selected exploratory correlations for patients with DM1. Because the ROI data suggested profound white matter abnormalities across the cerebrum rather than a regionally specific effect, correlations were only computed between **whole-cerebrum** white matter integrity and the neurocognitive measures. To further limit the number of correlations examined, we focused on fractional anisotropy (FA), the most commonly used DTI index of white matter integrity. The results, listed in Table 7, suggest a relationship in the predicted direction between full-scale IQ and whole brain fractional anisotropy. Greater white matter abnormality (as indicated by lower FA) was associated with lower full-scale IQ. The data also suggest that executive functioning may be related to overall whole-cerebrum white matter integrity.

4. Discussion

These results suggest that young patients with early-onset DM1 have significant white matter abnormalities throughout the brain. Low FA was observed in inferior frontal, superior frontal, occipital, and supracallosal regions, indicating that the abnormalities in DM1 are diffuse as opposed to regionally specific. Very few studies have examined white matter microstructure using DTI in patients with myotonic dystrophy and we believe that this is the first study to specifically do so in child and adolescent patients. Takaba et al. [42] first demonstrated widespread white matter diffusion abnormalities in adult patients with myotonic dystrophy. The same group reported lower FA and higher mean diffusivity (MD) in both hyperintense white matter lesions and in the normal-appearing white matter in patients with myotonic dystrophy compared to control subjects [32]. Ota et al. [33] examined white matter in several corpus callosum tracts using DTI and found lower FA and higher MD in the genu, rostral body, anterior midbody, posterior midbody, and splenium tracts. They found evidence of grey matter atrophy specifically in bilateral cortical regions that would be connected by the affected corpus callosum fibers. The authors suggested that the DTI changes could be related to Wallerian degeneration of the white matter following atrophy in the cortical grey matter.

Unfortunately, the biophysical meaning of diffusion abnormalities in white matter is not yet fully understood. Initially, it was thought that myelin was the primary contributor to anisotropy in normal axons and diffusion abnormalities might specifically reflect myelin disruption [43]. However, a number of studies have shown that myelin's role in anisotropy is minor [44,45]. A number of other microstructural factors contribute significantly to diffusion anisotropy. The axonal membrane itself and the longitudinally-oriented microtubules and neurofilaments that are part of the structure of axons are known to be important in anisotropy [46,47]. Also, fast axonal transport within the cell may accentuate diffusion, as measured by DTI, in the long axis direction of the axon [46]. Finally, the diffusion of extra-axonal water between densely packed axons is another important contributing factor to anisotropy. Thus, a number of possible changes to the white matter microstructure could lead to the diffusion abnormalities seen in DM1 in the current study.

Although FA has been the most commonly reported DTI measure, the additional measures of axial, radial, and mean diffusivities are also potentially useful in characterizing different aspects of white matter status. In mice, Song et al. [48] found that dysmyelination was reflected in increased radial diffusivity but no change in axial diffusivity. In a mouse model of ischemia, optic nerve axonal degeneration was associated with a selective decrease in axial diffusivity [49]. Demyelination, which occurred later, was reflected in a subsequent increase in radial diffusivity. Thus, the axial diffusivity measure may be particularly sensitive to damage to the axon itself, whereas radial diffusivity may be sensitive to abnormalities in the myelin sheath surrounding the axon. These studies point out that various DTI measurements may be *differentially sensitive* to the various points in the sequence of white matter damage. The current finding of abnormalities in all four DTI measures in young patients with DM1 could possibly reflect the accumulated series of changes that have already taken place in the white matter by the time the measurements were taken. Alternatively, significant changes to either intracellular or extracellular water content could also lead to changes in axial and radial diffusivity measures.

Establishing links between neuroimaging findings and cellular changes in DM1 is a major challenge. Neuronal migration errors have been observed in congenital-onset DM1 as have ventricular enlargement, corpus callosum hypoplasia, periventricular leucomalacia, and cortical atrophy [21,22,50] but these findings are variable and some studies have shown no specific brain pathology in congenital-onset DM1 [51,52]. DiCostanzo et al. [27] have suggested that white matter pathology, including myelin abnormalities, may have been historically underestimated in pathological studies of DM1. They have provided evidence of diffusely increased T2 relaxation times in DM1, perhaps resulting from alterations in myelin and changes in inter-axonal water content [31]. Myelin abnormalities in DM1 have also been potentially implicated by evidence of widespread magnetization transfer imaging (MTI) abnormalities (low magnetization ratio) in normal-appearing white matter [30,53].

Disease progression in DM1 has been associated with widespread cell loss in both subcortical and cortical grey matter [25,54–57], but this quantification is difficult. MRI voxel-based morphometry studies corroborate these findings of atrophy in multiple brain regions [10,27,58–60]. DM1 pathology also involves neuronal inclusions (ribonuclear inclusions with co-aggregated muscleblind protein; intracytoplasmic inclusion bodies) in multiple brain regions that may also play a role in functional cognitive disturbances [61–66]. Specifically relevant to the current study are findings of RNA foci in various locations throughout the brain including subcortical white matter and corpus callosum [63].

The clinical implications of white matter disruption in DM1 have been explored, but the findings have been somewhat inconsistent. Some studies find direct association with cognitive disturbance [14,26,67] while others do not [8,23,68]. Much of the literature to this point has focused on white matter hyperintensities, which occur in the majority of patients late in the course of the disease, especially in sub-cortical regions, but also elsewhere including temporal lobe [9,10,14,59,69]. In adults, white matter abnormalities have been shown to be associated with intellectual dysfunction [10,14,29], psychomotor speed [70], verbal fluency [67], attention [67]. At least one study has demonstrated that the degree of cognitive deficit may depend on the specific location of the white matter damage in DM1; Damian et al. [71] posit that intellectual impairment is greater in patients with damage to the white matter adjacent to cortex in contrast to patients with primarily sub-cortical white matter changes.

Consistent with the literature on cognitive functioning in DM1 [11], we observed overall IQ deficits in young patients with early onset disease. We did not observe significant executive functioning deficits or memory deficits, which are classically evident in adults [17–19] and

which have been seen in adults who had early-onset DM1[13]. However, parent ratings of executive functioning did show evidence of problems with “real world” executive skills such as planning, organizing, and self-monitoring. Both the neurocognitive test data and the imaging data suggest that the neuropathology in these patients was diffuse rather than focal. Cerebral FA correlated significantly with full-scale IQ, which is a global measure of cognitive status. Furthermore, an examination of the correlations between cerebral FA and the individual Wechsler index measures suggests relatively strong associations with all four indexes, although the small sample size precludes these associations from reaching significance. In the future, larger numbers of participants may allow for a more targeted examination of regional white matter abnormalities and specific cognitive deficits.

In conclusion, the current study provides evidence of widespread white matter abnormalities in multiple brain regions in young patients with early-onset DM1. These abnormalities correlate with important aspects of cognitive functioning, most notably intelligence and executive functioning. Several DTI measures were abnormal, suggesting significant microstructural deficits not limited to myelin and, perhaps, reflecting an accumulation of changes that have occurred over time. Future studies could build on these findings by collecting similar measures earlier in the disease process and obtaining the measures at several time points across development.

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Figure 1. Masks defining three Regions of Interest (ROIs) on T1-weighted images; Blue = superior-frontal mask; Yellow = inferior-frontal mask; Red = occipital mask.

Figure 2. Mask defining the fourth Region of Interest (ROI) on T1-weighted images; Green = supracallosal mask.

Table 1

Subject characteristics for eight participants with Myotonic Dystrophy Type 1.

Subject	Age	Sex	Trans- mission	Onset	CTG Repeats	VCI	PRI	WMI	PSI	FSIQ
1	12	Male	Maternal	Congenital	> 600	73	92	74	78	74
2	14	Female	Maternal	Congenital	> 600	73	73	80	65	67
3	15	Male	Maternal	Congenital	≈1700	65	51	52	62	48
4	10	Female	Paternal	Juvenile	≈600	85	69	91	85	77
5	12	Female	Paternal	Juvenile	≈430	102	104	110	85	102
6	15	Male	Paternal	Juvenile	≈590	99	77	80	65	77
7	15	Male	Paternal	Juvenile	≈375–500	61	69	65	75	60
8	17	Female	Maternal	Juvenile	≈200	91	115	86	91	95

Note: Exact CTG repeat counts were not available for subject #1 and #2 due to the inexact nature of southern blot analysis.
Note: VCI = Wechsler Verbal Comprehension Index; PRI = Perceptual Reasoning Index; WMI = Working Memory Index; PSI = Processing Speed Index; FSIQ = Full Scale Intelligence Quotient.

Table 2

Neuropsychological results by group.

Measure	<u>Control</u>	<u>DM1</u>	Significance (p)
	Mean (SD)	Mean (SD)	
Wechsler Verbal Comprehension	104.1 (13.9)	81.1 (15.4)	.007
Wechsler Perceptual Organization	100.9 (10.8)	81.2 (20.9)	.034
Wechsler Working Memory	101.4 (10.4)	79.8 (17.3)	.009
Wechsler Processing Speed	102.3 (7.6)	75.8 (10.9)	<.001
Full-Scale IQ	103.1 (10.8)	75.0 (17.6)	.002
California Verbal Learning Test (total)	51.9 (8.4)	44.6 (12.7)	.200
Wisconsin Card Sorting Test (total errors)	97.8 (20.4)	88.0 (23.2)	.387
BRIEF General Executive Composite	46.3 (6.2)	66.4 (8.2)	<.001

Note: All tests were administered to all subjects.

Note: SD = Standard Deviation.

Table 3

Inferior frontal white matter group comparisons.

Measure	<u>Control</u>	<u>DM1</u>	Significance (p)
	Mean (SD)	Mean (SD)	
Fractional Anisotropy	.393 (.017)	.312 (.031)	<.0001
Mean Diffusivity $\times 10^{-3}$	.825 (.021)	.942 (.054)	<.0001
Radial Diffusivity	.645 (.021)	.784 (.063)	<.0001
Axial Diffusivity	1.18 (.028)	1.26 (.044)	.001

Note: SD = Standard Deviation.

Table 4

Superior frontal white matter group comparisons.

Measure	<u>Control</u>	<u>DM1</u>	Significance (p)
	Mean (SD)	Mean (SD)	
Fractional Anisotropy	.394 (.013)	.312 (.033)	<.0001
Mean Diffusivity $\times 10^{-3}$	.793 (.019)	.919 (.051)	<.0001
Radial Diffusivity	.619 (.021)	.769 (.062)	<.0001
Axial Diffusivity	1.14 (.021)	1.21 (.034)	<.0001

Note: SD = Standard Deviation.

Table 5

Supracallosal white matter group comparisons.

Measure	<u>Control</u>	<u>DM1</u>	Significance (p)
	Mean (SD)	Mean (SD)	
Fractional Anisotropy	.376 (.019)	.309 (.031)	.0001
Mean Diffusivity $\times 10^{-3}$	.795 (.020)	.892 (.051)	.0002
Radial Diffusivity	.626 (.025)	.743 (.059)	.0001
Axial Diffusivity	1.13 (.017)	1.19 (.050)	.008

Note: SD = Standard Deviation.

Table 6

Occipital white matter group comparisons.

Measure	<u>Control</u>	<u>DM1</u>	Significance (p)
	Mean (SD)	Mean (SD)	
Fractional Anisotropy	.419 (.019)	.334 (.033)	<.0001
Mean Diffusivity $\times 10^{-3}$	.792 (.018)	.892 (.056)	.0003
Radial Diffusivity	.596 (.024)	.725 (.062)	<.0001
Axial Diffusivity	1.18 (.010)	1.23 (.055)	.04

Note: SD = Standard Deviation.

Table 7

Correlations between whole-brain fractional anisotropy and cognition for patients in the DM1 group (n = 8).

Measure	Pearson correlation (r) & significance (p)
WISC-IV Verbal Comprehension	.55 (.16)
WISC-IV Perceptual Organization	.70 (.06)
WISC-IV Working Memory	.64 (.09)
WISC-IV Processing Speed	.65 (.09)
Full-Scale IQ	.74 (.04)
California Verbal Learning Test Total	.24 (.57)
Wisconsin Card Sorting Test (errors)	.70 (.05)
BRIEF exec. functioning (parent report)	-.39 (.34)