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Anomalous Putamen Volume in Children with Complex Motor Stereotypies

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Abstract

Introduction—Complex motor stereotypies in children are repetitive, rhythmic movements that have a predictable pattern and location, seem purposeful, but serve no obvious function, tend to be prolonged, and stop with distraction, e.g., arm/hand flapping, waving. They occur in both “primary” (otherwise typically developing) and secondary conditions. These movements are best defined as habitual behaviors and therefore pathophysiologically hypothesized to reside in premotor to posterior putamen circuits. This study sought to clarify the underlying neurobiological abnormality in children with primary complex motor stereotypies using structural neuroimaging, emphasizing brain regions hypothesized to underlie these atypical behaviors.

Methods—High-resolution anatomical MRI images, acquired at 3.0T, were analyzed in children ages 8–12 years (20 with primary complex motor stereotypies, 20 typically developing). Frontal lobe sub-regions and striatal structures were delineated for analysis.

Results—Significant reductions ($p=0.045$) in the stereotypies group were identified in total putamen volume, but not caudate, nucleus accumbens or frontal sub-regions. There were no group differences in total cerebral volume.

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Conclusion—Findings of a smaller putamen provide preliminary evidence suggesting the potential involvement of the habitual pathway as the underlying anatomical site in primary complex motor stereotypies.

Keywords

Motor stereotypies; habitual behaviors; goal-directed behaviors; childhood; movement disorders

Introduction

Motor stereotypies are defined in this report to be repetitive, rhythmic movements that have a predictable pattern and location, seem purposeful but serve no obvious function, tend to be prolonged, and stop with distraction, e.g., arm/hand flapping, waving, and begin before age 3 years¹. While previously thought to be solely associated with intellectual disability, sensory deprivation, or autism spectrum disorders, complex motor stereotypies (CMS) are now recognized to occur in a more “primary” form in otherwise typically developing children, affecting as many as 3–4% in early childhood². These movements begin in infancy, persist into adulthood, and lead to psychosocial³ and neuromotor difficulties⁴.

The pathophysiology of primary CMS is unknown. Unlike voluntary movements, stereotypies are not preceded by movement-related cortical potentials⁵. Proposed hypotheses have suggested an alteration within cortico-striato-thalamo-cortical circuits or interconnecting regions¹. Anatomically, distinct cortical-striatal pathways have been associated with *goal-directed* and *habitual* behaviors¹. Goal-directed action is mediated via a ventromedial prefrontal cortex to caudate pathway², whereas habitual behavior involves a premotor to posterior putamen circuit³. In a small neuroimaging study of 6 boys with primary CMS, volumetric reductions (compared to typically developing boys) were identified in the caudate and frontal white matter⁴. A recent study of 20 primary CMS children, using ¹H-MR spectroscopy, identified a significant reduction of GABA in the striatum and anterior cingulate cortex, but not prefrontal cortex⁵.

The goal of this study was to determine whether children with primary CMS manifest greater structural anomalies in cortico-striato-thalamo-cortical brain regions emphasizing comparisons between habitual and goal-directed circuits. Because habitual movements are hypothesized to reside pathophysiologically premotor to posterior putamen circuits, these regions were emphasized in analyses.

METHODS

Study Procedures

Approval was granted from the Johns Hopkins Medicine Institution Review Board. Parents of all participants provided written consent and all participants provided assent.

Participants

Participants with CMS (ages 8–12 years) were recruited from the Johns Hopkins Pediatric Movement Disorder Clinic or associated website (www.hopkinsmedicine.org/neuro/

stereotypy) and directly assessed by a child neurologist with expertise in pediatric movement disorders (HSS). Evaluation, including direct observation or video provided by parents, confirmed the presence of CMS. Participants were excluded if there was a history of motor/vocal tics; but not excluded if they had co-occurring Attention-deficit/Hyperactivity Disorder (ADHD) or Obsessive Compulsive Disorder. The rationale for excluding individuals with tic disorders was twofold: 1) both disorders are proposed to involve habitual pathways^{6, 7}, and, 2) prior reports in Tourette syndrome suggest alterations involving both the putamen and caudate nucleus. For example, volumetric MRI studies in individuals with Tourette syndrome have shown smaller caudate volumes bilaterally (which did not correlate with symptom severity) and variable changes in the putamen (reduced, larger, or changes in symmetry)⁸. All participants in the CMS group were screened for autistic spectrum disorder and excluded if they had a score greater than 13 on the Autism Spectrum Screening Questionnaire⁹.

Typically developing participants were recruited from the community as part of ongoing studies, and matched individually by age, sex, handedness, and IQ to children in the CMS group. Additional exclusion criteria for both CMS and typically developing groups included current IQ < 80, diagnosis of autism spectrum disorder, visual impairment, treatment with psychotropic medications in the past three months, neurological disorder (e.g., epilepsy, cerebral palsy, and traumatic brain injury), hearing loss > 25 dB, and a medical contraindication to MRI procedures. The sample included 20 children with primary CMS (12 boys, 8 girls) and 20 typically developing controls (12 boys, 8 girls).

Study Measures

Presence of a psychiatric diagnosis was assessed using the Diagnostic Interview for Children and Adolescents-4th Edition¹⁰. Full Scale IQ was measured by the Wechsler Intelligence Scale for Children-IV¹¹ or Stanford-Binet Intelligence Scales—Fifth Edition¹². ADHD symptoms were assessed using the ADHD Rating Scale-IV¹³.

Stereotypy severity was rated by parents using the Stereotypy Severity Scale¹⁴, a caregiver questionnaire patterned after the Yale Global Tic Severity Scale and designed to measure stereotypic movements rather than tics. The scale consists of two components, one pertaining to the motor dimensions of the movement and the other pertaining to the global effects of the movement. The motor component rates the movement along four discriminate dimensions, including number (0–3 points), frequency (0–5 points), intensity (0–5 points), and interference (0–5 points), for a total of 18 points. An independent rating of global impairment caused by the movement (up to 50 points) is added to obtain the total score (maximum 68 points); higher score indicating a greater severity of stereotypic movements.

Imaging Protocol

All participants were provided mock scan sessions to decrease anxiety and train them to lie still. No sedation was used. Magnetic resonance images were acquired on a 3.0T Philips Achieva MRI scanner. Magnetization Prepared Rapid Gradient Recalled Echo (MPRAGE) images (slice thickness=1.0 mm; FOV=26 cm; matrix size: 256×256) were used for volumetric assessment and analysis of macroscopic features of the cortex. Atlas-based

regions of interest (ROIs) and total cerebral volume measurements were obtained using FreeSurfer.

Within FreeSurfer, frontal lobe ROIs were parcellated and delineated using an automated frontal lobe atlas, based on functionally distinct ROIs that were manually delineated using a pediatric population. Specifically, the ROIs were delineated on the bases of consistent sulcal-gyral landmarks chosen because of their relationships to functional boundaries indicated by cytoarchitectonic, electrophysiological, magnetic stimulation, and functional imaging findings. The detailed procedures for frontal lobe parcellation used in the present study, along with a figure outlining the regions, are referenced in Ranta et al.¹⁵

The resulting frontal lobe atlas included left and right hemisphere anterior cingulate (ACC), dorsolateral prefrontal cortex (DLPFC), medial prefrontal cortex (mPFC), inferior lateral prefrontal cortex (ILPFC), medial orbitofrontal cortex, lateral orbitofrontal cortex, frontal eye field (FEF), lateral premotor cortex (LPM), supplementary motor complex (SMC), and primary motor cortex (M1). For the present study, ROIs were combined to permit examination of *prefrontal* (DLPFC, mPFC, ILPFC, lateral OFC, medial OFC), *premotor* (FEF, LPM, and SMC) cortex collectively; ACC and M1 were analyzed separately.

The structures of the striatum were traced manually by two experienced raters using MIPAV (Medical Image Processing and Visualization). The caudate nucleus (including the nucleus accumbens), and putamen were outlined on contiguous coronal slices. The manual protocol attempted to separate the nucleus accumbens from the caudate, using a cut plane to define the superior boundary of the nucleus accumbens. To balance the competing priorities of validity and reliability, cut planes were used when the level of anatomical detail in MR images or degree of inter-subject variability made the use of standard anatomical landmarks excessively difficult. Detailed tracing guidelines, along with a figure depicting the regions, are described in a previously published manuscript¹⁶. Intra-rater reliability was established for each region on five scans measured twice by the same rater (rater 1). Inter-rater reliability was established by a second rater and calculated using the time 2 measures from rater 1. Intraclass correlation coefficients (ICC) revealed high rates of intra- and inter-rater reliability for the caudate (intra 0.96; inter 0.92), putamen (intra 0.98; inter 0.93) and globus pallidus (intra 0.96; inter 0.90).

Statistical Analyses

Group comparisons for regional volumes were made between children with CMS and controls for total cerebral volume, frontal sub-regions, and striatum. For those regions in which significant group differences were observed, brain-behavior correlations were examined using associations with stereotypy severity and ADHD symptoms.

RESULTS

Sample Demographics

Both groups included 12 boys and 17 right-handed children. There were no significant differences in age, Full Scale IQ, or racial distribution [$\chi^2(2)=1.38$, $p=0.517$] between the CMS and control groups (Table 1). Children in the CMS group were rated by parents as

having significantly greater symptoms of ADHD; however, based on results of the structured psychiatric interview, none of the children in either group met criteria for any psychiatric diagnosis, including ADHD.

Group Comparisons for Frontal and Striatal Volumes

There were no significant group differences in total cerebral volume (TCV) [$F(1,38)=0.19$, $p=0.662$, $\eta^2_p=0.005$]. Within frontal sub-regions (PFC, PMC, ACC, M1), and striatal structures, left vs. right hemisphere volumes in each group were all significantly correlated (all $r>0.30$, $p<0.05$), and as such, left and right hemisphere volumes were combined by adding left and right hemisphere values for subsequent analyses. Within frontal lobe subdivisions, after controlling for TCV, there was no significant group difference for PMC, PFC, ACC or M1 volumes (Table 2). Within the caudate, nucleus accumbens, and putamen, left vs. right hemisphere volumes were highly correlated (all $r>0.90$), and as such, volumes for left and right hemispheres were combined for between group analyses. After controlling for TCV, the CMS group showed significant reductions in total putamen ($p=0.045$; see Figure 1), but not caudate ($p=0.629$) or nucleus accumbens ($p=0.748$).

Brain-Behavior Correlations

Brain-behavior associations were examined within the CMS group. Neither SSS Motor ($r=0.100$, $p=0.690$), SSS Impairment ($r=0.311$, $p=0.209$), nor ADHD symptoms ($r=0.234$, $p=0.349$) were significantly associated with total putamen volume.

DISCUSSION

The present study represents the largest cohort of children to date, with carefully diagnosed primary complex motor stereotypies who have undergone anatomic MRI analyses to examine brain structures within cortico-striato-thalamo-cortical circuitry. Findings identified a significant reduction in the size of the putamen, with no significant change in the caudate, frontal sub-regions, total cerebral volume, or the presence of an anomalous cortical structure. These findings are generally consistent with results identified in a younger cohort of children with primary CMS (ages 5–9 years) evaluated by single voxel MR spectroscopy. In the latter, affected children had a significant reduction of GABA, the inhibitory neurotransmitter of striatal projection neurons and striatal and cortical interneurons, within both the striatum and ACC, but not prefrontal or premotor cortex⁵. In contrast, our larger sample, including both boys and girls, differ from a smaller earlier study of solely boys with primary CMS⁴, which showed a reduction in caudate and frontal white matter volumes. The differences in findings in the present study may be related to larger sample size, the inclusion of both boys and girls, greater control of comorbidities, or MR scanning at 3.0T, rather than 1.5T. Similar the current findings, the earlier study of boys with primary CMS⁴ did not identify frontal gray matter reductions in the CMS group, but rather, showed reductions only in white matter volume.

The present results add to the greater understanding of the neural substrate of habitual behaviors. A habit is a repetitive, fixed, purposeful movement that is performed automatically, is slow to change, is elicited by a particular context or stimulus, driven by

reinforcement, stimulus-responsive, and one that does not occur in relation to a current or future goal. In the rodent, which contains an undifferentiated striatum, localized pathways are *goal-directed* (orbitofrontal and prefrontal pathways to the dorsomedial striatum) and *habit* associated (sensorimotor cortex to dorsolateral striatum). Damage to the dorsolateral striatum affects the acquisition of stimulus–response associations¹⁷. Studies in humans, some involving the use of fMRI, have shown that the posterolateral putamen corresponds functionally to the dorsolateral striatum in rodents³. More specifically, investigations measuring white matter tract strength have shown that tasks resulting from competition between habitual and goal-directed action was predictable by tracts involving the posterior putamen¹⁸. In animal models, it has been further suggested that the infralimbic cortex provides a condition that builds and permits habitual behaviors¹⁹.

The present findings add to the relatively small research literature on the neurobiology the full range of behavioral phenotypes, neuroimaging biomarkers, and genotypes of CMS. Further, to date, there have no identified effective pharmacotherapies identified for individuals with primary CMS²⁰, nor has there been adequate investigation of existing comorbidities. Thus, the identification of specific structural abnormalities within the brain, especially in habitual pathways, may enable us to better appreciate the underlying neurobiological mechanism and can help direct future studies designed develop better therapies for the condition.

In this report, the lack of an association between putamen volume and stereotypy severity was unexpected. Prior studies in younger children with primary CMS⁵ have shown a positive association between striatal GABA/Cr and SSS severity (but not ACC), perhaps suggesting the presence of a critical reduction in striatal projection neurons, beyond which there is no further impact on stereotypies. An additional potential explanation is that the expected correlation represents a developmental phenomenon, i.e., neurobiological changes associated with repetitive behavior may evolve over time. For example, in functional connectivity studies, the strength of association between the putamen and motor cortex diminishes with maturation, while simultaneously connectivity becomes progressively stronger within regions supporting controlled attention (e.g., fronto-parietal cortex)²¹. It is also possible that other essential connections, not measured in this protocol, are critical in the neurobiology of CMS. For example, the ventral striatum, which receives input from the limbic circuit, amygdala and hippocampus, has an important integrative role for information relating to emotion, vigor, reward, attention and autonomic factors. Further, there is new evidence for the involvement of the globus pallidus externa and interna^{22, 23} and cerebellum²⁴.

These preliminary findings, while promising, should be considered along with several study limitations. Although the sample size represents the largest anatomical MRI examination in children with carefully characterized primary CMS, the actual number is relatively small and numerous potential regions of interest were not investigated. Nevertheless, given the findings of a reduced putamen volume in children with primary CMS, additional analyses emphasizing differences in basal ganglia shape^{16, 25} or combining various methodologies in the same sample (e.g., structural MRI, MR spectroscopy, diffusion tensor imaging, functional connectivity) are likely to provide additional insight into the unique neurobiology of primary CMS.

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Figure 1.

Total putamen volume (combining left and right hemispheres) is significantly reduced in children with primary complex motor stereotypies (ages 8–12 years), compared to age- and sex-matched typically developing children ($p < .05$).

Table 1

Participant Demographics

	Control (<i>n</i> = 20)		CMS (<i>n</i> = 20)		<i>p</i>	η^2_p
	Mean	SD	Mean	SD		
Age	9.36	1.07	9.39	1.24	0.933	0.001
FSIQ	108.40	12.00	102.79	14.78	0.200	0.044
Inattention	1.95	2.76	7.33	6.26	0.001	0.253
Hyperactivity	1.850	2.18	4.28	2.93	0.006	0.191

Note: FSIQ = Full Scale IQ score from either the Stanford Binet-5, or the Wechsler Intelligence Scale for Children, Fourth Edition (WISC-IV); Inattention = Inattention total raw score from ADHD Rating Scale=IV; Hyperactivity = Hyperactivity raw score from the ADHD Rating Scale-IV.

Table 2

Group Means for Volumes within CTSC Circuitry

	Control (<i>n</i> = 20)		CMS (<i>n</i> = 20)		<i>p</i>	η^2_p
	Mean	SD	Mean	SD		
Total Caudate	8978.85	1123.89	8853.95	1348.16	0.629	0.006
Total Nucleus Accumbens	498.60	167.34	476.10	174.61	0.748	0.003
Total Putamen	9840.65	1110.92	9310.15	941.59	0.045	0.104
Total Premotor	32405.80	2736.89	32840.15	2880.59	0.661	0.005
Total Prefrontal	135469.65	11797.87	134763.10	14012.08	0.494	0.013
Total ACC	14415.15	2183.46	14555.70	1726.47	0.930	<0.001
Total M1	26755.90	3102.24	27175.75	2669.33	0.640	0.006

Note: Total volumes for regions of interest are in mm³, combining left and right hemispheres. Group differences in regional volumes are compared while controlling for total cerebral volume. Total premotor cortex includes: frontal eye fields, lateral premotor cortex, and supplemental motor cortex. Total prefrontal cortex includes: dorsal lateral prefrontal cortex, medial prefrontal cortex, inferior lateral prefrontal cortex, lateral orbitofrontal cortex, medial orbitofrontal cortex. M1 = primary motor cortex.