Frontal White Matter Reductions in Healthy Males With Complex Stereotypies

Wendy R. Kates, PhD*,†, Diane C. Lanham, MA‡, and Harvey S. Singer, MD§

The pathophysiologic mechanism for stereotypic, bilateral repetitive movements involving the arms and hands (complex motor stereotypies) is unknown. This study used volumetric magnetic resonance imaging to compare cerebral lobes and caudate nucleus in six males with complex stereotypies and average intelligence to age-matched control subjects. Results indicated volumetric reductions in frontal white matter, disproportionate to total cerebral white volume, and in the left and right caudate nuclei. These preliminary data suggest a possible dysfunction of cortico-striatal-thalamo-cortical circuitry in children with nonautistic, physiologic motor stereotypies. © 2005 by Elsevier Inc. All rights reserved.


Introduction

Repetitive movements involving the hands and arms (e.g., recurrent arm flapping, hand waving/rotating, finger wiggling) often occur in children with autism, mental retardation, and sensory deprivation but can also be observed in otherwise healthy infants and children. These movements, known as motor stereotypies, are clinically defined by their involuntary, patterned, coordinated, repetitive, rhythmic, nonreflexive actions and predictable form, amplitude, and location. They typically last from seconds to minutes, tend to occur in clusters, appear many times per day, and, like complex motor tics, can be associated with periods of excitement, stress, fatigue, or boredom. However, they can be differentiated from complex motor tics by virtue of the fact that their age of onset is earlier than motor tics, and they are more rhythmic, fixed in pattern, and prolonged than motor tics. Unlike complex motor tics, motor stereotypies are readily suppressed by sensory stimuli or distraction and are usually of little concern to the patient [1,2]. Physiologic stereotypies, that is those occurring in the absence of other neurologic or behavioral findings, have been subdivided into three subgroups, complex (primarily arms and hands), head nodding, and common stereotypies (body rocking, biting).

The underlying biologic mechanism for stereotypic repetitive movements in children is unknown. Neuroanatomically, cortico-striatal-thalamo-cortical circuits have been identified as the site of abnormality in other pediatric movement disorders, including tics and chorea [3]. In a rodent model, pharmacologic activation of dopamine receptors in specific regions of the caudoputamen (striatum) produces several different stereotypies [4,5]. Animal studies have also demonstrated that activity in the striosomal rather than matrix portion of the striatum, especially in the anterior and lateral (sensorimotor) region, is an excellent predictor of the amount of stereotypy [6].

In a pilot effort to identify structural alterations in cortical and striatal regions of the brains of otherwise healthy children with complex stereotypies, anatomic magnetic resonance imaging was used in this study to measure volumes of the cerebral lobes and the caudate nucleus.

Methods

Participants were six males with complex stereotypies, mean age 9.9 years, and six males without stereotypies, individually matched by age (mean age 10.2 years) (Table 1). Children with stereotypies were recruited from a child neurology clinic in a large, urban hospital. Extensive clinical evaluation and assessment of each patient was conducted by a pediatric neurologist (H.S.S.), indicating that these were otherwise healthy children attending regular classrooms with no clinical
Evidence of autism, pervasive developmental disorder, psychiatric or neurologic dysfunction. Control subjects were recruited from the office of a local pediatrician, initially screened to exclude neurologic dysfunction or developmental delay, and included in the final sample if they scored within the average range on a standardized intelligence test and behavioral checklists completed by parents.

Coronal magnetic resonance images of each subject’s brain were acquired with a three-dimensional volumetric radiofrequency spoiled gradient echo series (echo time = 5-7 ms; repetition time = 35-45 ms; flip angle = 45°) of 124, 1.5-mm contiguous slices. The image data were imported into the imaging software program BrainImage for measurement. The isolated brain tissue was subdivided into cerebral lobes according to a revised Talairach stereotaxic grid specific for measurement in pediatric study groups. Each region was then segmented into gray, white, and cerebrospinal fluid compartments using an algorithm that assigns voxels to one or more tissue categories based on intensity values and tissue boundaries. The caudate nucleus was manually measured on each scan by raters blind to the diagnosis of the subject.

Because of the small size of the study groups, nonparametric methods of analysis with the Mann-Whitney U Test were used for inter-group comparisons. Comparisons were conducted in the following sequence:

1. Volumes of cerebral gray and cerebral white matter, and the caudate nucleus, were compared between patients and control subjects.
2. If the volumes of either gray or white compartments of the total cerebrum differentiated patients from control subjects, the volumes of respective (gray or white) lobar compartments were compared between patients and control subjects.

Table 1. History and clinical characteristics of stereotypy patients

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Sex</th>
<th>Age at Onset</th>
<th>Movements</th>
<th>Triggers</th>
<th>ADHD/OCD/Medication</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>9.3</td>
<td>M</td>
<td>2 yr</td>
<td>Finger wiggling in front of face</td>
<td>Excitement, nervous</td>
<td>Yes/No/Methylphenidate</td>
</tr>
<tr>
<td>2</td>
<td>10.3</td>
<td>M</td>
<td>6 mo</td>
<td>Arm stretching with hand clasping</td>
<td>Excitement, bored</td>
<td>No/No/No</td>
</tr>
<tr>
<td>3</td>
<td>7.4</td>
<td>M</td>
<td>2 yr</td>
<td>Arm and hand flapping</td>
<td>Excitement, bored</td>
<td>Yes/No/No</td>
</tr>
<tr>
<td>4</td>
<td>11.3</td>
<td>M</td>
<td>1 yr</td>
<td>Arm flapping</td>
<td>Engrossed, excitement</td>
<td>No/No/No</td>
</tr>
<tr>
<td>5</td>
<td>10.1</td>
<td>M</td>
<td>1 yr</td>
<td>Arm extension and rotation</td>
<td>Excitement</td>
<td>No/No/No</td>
</tr>
<tr>
<td>6</td>
<td>11.1</td>
<td>M</td>
<td>9 mo</td>
<td>Arm and hand flapping</td>
<td>Excitement, stress</td>
<td>No/No/No</td>
</tr>
</tbody>
</table>

Abbreviations:
ADHD = Attention-deficit-hyperactivity disorder
OCD = Obsessive-compulsive disorder
OT = Occupational therapy evaluation
ST = Speech therapy

Figure 1. Boxplot comparing frontal lobe white matter volumes of children with stereotypies to control subjects.
If the volumes of the (gray or white) compartments of a specific lobar region differentiated patients from control subjects, the corresponding ratio of lobar (white or gray) volume to cerebral (white or gray) volume was compared between patients and control subjects.

If the volumes of the caudate nucleus differentiated patients from control subjects, the ratio of the caudate nucleus volume to entire brain volume was compared.

Results

Relative to their age-matched peers, total cerebral white volumes were reduced \( (P < 0.03) \) by approximately 9% in males with stereotypies (Table 2). These reductions were due primarily to decreases in frontal \( (P = 0.009) \) and temporal \( (P = 0.04) \) white matter. Whereas temporal white reductions were not disproportionate to total cerebral white reductions, frontal white matter was significantly reduced when analyzed as an absolute volume and relative to total cerebral white volume \( (P < 0.03) \) (Fig 1). Frontal white matter loss reached 11.5% in males with stereotypies relative to unaffected peers. Group differences were not observed in absolute or relative frontal gray volumes, or in parietal, temporal, or occipital gray or white volumes.

Although the absolute volumes of the left \( (P = 0.04) \), right \( (P = 0.05) \), and total \( (P = 0.04) \) caudate nuclei were reduced in males with stereotypies, they were not reduced relative to total brain tissue volume (Table 2).

Discussion

The underlying pathophysiologic mechanism of stereotypies, especially in otherwise normal children, has not been extensively evaluated. Normal neuroradiographic and electroencephalographic studies, plus the high prevalence of complex stereotypies in autistic and retarded populations, has led many investigators to propose psychological hypotheses. In general, proponents have suggested two possibilities; a form of self-stimulation to compensate for a deficit of external arousal (e.g., congenital blindness, autism, or mental retardation), or an attempt to use up excess attention capacity or to reduce external distractions by channeling thoughts and actions into movements \[7,8\]. Others have conceptualized stereotypies as being related to obsessive-compulsive disorder, general anxiety disorder, perfectionism, or impulse dyscontrol. The presence of stereotypies in otherwise healthy children, however, challenges these hypotheses.

Reductions in total frontal white matter, measured as both an absolute volume and relative to total cerebral white volume, and changes in the absolute volume of

Table 2. Volumes (cc) of frontal lobe regions, cerebrum, and caudate nucleus*

<table>
<thead>
<tr>
<th>Brain Region</th>
<th>Stereotypy ((n = 6))</th>
<th>Control ((n = 6))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cerebrum total gray</td>
<td>696.65 ± 63.26</td>
<td>728.15 ± 51.56</td>
</tr>
<tr>
<td>Cerebrum total white†</td>
<td>436.60 ± 29.41</td>
<td>479.21 ± 26.62</td>
</tr>
<tr>
<td>Frontal lobe gray</td>
<td>255.23 ± 22.44</td>
<td>258.93 ± 23.98</td>
</tr>
<tr>
<td>Parietal lobe gray</td>
<td>170.27 ± 22.21</td>
<td>177.23 ± 14.06</td>
</tr>
<tr>
<td>Temporal lobe gray</td>
<td>151.75 ± 11.51</td>
<td>159.38 ± 12.53</td>
</tr>
<tr>
<td>Occipital lobe gray</td>
<td>77.63 ± 7.08</td>
<td>86.11 ± 5.51</td>
</tr>
<tr>
<td>Frontal lobe white‡</td>
<td>162.48 ± 10.75</td>
<td>183.81 ± 13.85</td>
</tr>
<tr>
<td>Parietal lobe white</td>
<td>123.35 ± 10.49</td>
<td>133.44 ± 11.11</td>
</tr>
<tr>
<td>Temporal lobe white‡</td>
<td>56.35 ± 4.63</td>
<td>64.48 ± 7.02</td>
</tr>
<tr>
<td>Occipital lobe white</td>
<td>51.65 ± 2.69</td>
<td>52.99 ± 3.55</td>
</tr>
<tr>
<td>Caudate nucleus (total)§</td>
<td>7.35 ± 1.70</td>
<td>9.38 ± 1.57</td>
</tr>
</tbody>
</table>

* Statistical comparisons were based on the Mann-Whitney test. Correction for multiple comparisons indicated that the threshold for a significant \( P \) value was 0.01. \( P \) values between 0.01 and 0.05 were considered statistical trends.

† Absolute volume comparison, \( P < 0.05 \).

‡ Absolute volume comparison, \( P < 0.01 \).

§ Relative volume (frontal white/cerebral white) comparison, \( P < 0.05 \).
caudate nuclei suggest involvement of cortico-striatal-thalamo-cortical circuits in complex motor stereotypies. These results, although preliminary in nature and limited by the small number of patients, have similarities to another paroxysmal childhood movement disorder, Tourette syndrome. In Tourette syndrome, which is characterized by the presence of motor and vocal tics, volumetric reductions are present in the striatum [9-12] and differences in cortical white matter have ranged from reductions in the deep left frontal white matter to increases in the left frontal lobe [13,14]. Changes in white matter, especially deep white matter, are suggestive of abnormalities in long association and projection fiber bundles. In stereotypies, both striatal changes and alterations of pathways that innervate the striatum can influence the production of movements. For example, studies in rodents of the inducibility of immediate-early genes for the Fos/Fra family of transcription factors have led to identification of the relative importance of striosomes in the production of stereotypies [6]. Additionally, in animal models, inputs from the frontal lobe, via fronto-subcortical circuits, have inhibited the dopamine-dependent induction of stereotypies [15].

Although numerous neurotransmitters participate in the cortico-striatal-thalamo-cortical circuits, the dopaminergic system has been demonstrated to have a major role in the production of stereotypies [4,5,16]. In animal models, stereotypic behaviors can be induced in response to directly acting dopamine agonists (apomorphine) or to indirectly acting dopamine receptor agonists (amphetamine, cocaine). Striosomes, the region implicated in stereotypies, send afferent projections to the dopaminergic-containing part of the substantia nigra (pars compacta) and, in turn, have a direct influence on striatal dopamine innervation. This exploratory study does have several limitations. The small sample size and the multiple comparison analyses clearly dilute the robustness of the reported associations. In addition, similar to a prior report of normal children with stereotypies [2], a subset of patients had a history of mild motor/language delays. Although we have no evidence suggesting that mild transient delays are associated with frontal white matter reductions, this possibility cannot be refuted. Although the presence of attention-deficit hyperactivity disorder in two patients may place further limitations on the significance of our findings, it is noteworthy that frontal and cerebral white volumes of the patients with attention-deficit hyperactivity disorder were larger than the frontal and cerebral group means for the total sample of males with stereotypies. Hence, we believe it is unlikely that morphologic alterations associated with comorbidity for attention-deficit hyperactivity disorder (which may include frontal white matter reductions) account for our findings.

In conclusion, volumetric reductions in the frontal white matter and caudate nuclei provide a preliminary understanding of the physiologic basis of complex motor stereotypies in otherwise healthy children. These results clearly challenge the notion that such movements are psychologically based. These data also provide the rationale for future hypothesis-driven neuroimaging studies containing larger, sex-mixed samples that include children with other forms of physiologic and pathologic stereotypies. Greater understanding of the underlying pathophysiology of stereotypies could lead to a greater understanding of developmental biology and pharmacologic interventions.

References