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Basal ganglia morphometry and repetitive behavior in young children with autism spectrum disorder

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Scientific Abstract

We investigated repetitive and stereotyped behavior (RSB) and its relationship to morphometric measures of the basal ganglia and thalami in 3-4 year old children with autism spectrum disorder (ASD; n=77) and developmental delay without autism (DD; n=34). Children were assessed through clinical evaluation and parent report using RSB-specific scales extracted from the Autism Diagnostic Observation Schedule (ADOS), the Autism Diagnostic Interview, and the Aberrant Behavior Checklist. A subset of children with ASD (n=45), DD (n=14) and a group of children with typical development (TD; n=25) were also assessed by magnetic resonance imaging (MRI). Children with ASD demonstrated elevated RSB across all measures compared to children with DD. Enlargement of the left and right striatum, more specifically the left and right putamen, and left caudate, was observed in the ASD compared to the TD group. However, nuclei were not significantly enlarged after controlling for cerebral volume. The DD group, in comparison to the ASD group, demonstrated smaller thalami and basal ganglia regions even when scaled for cerebral volume, with the exception of the left striatum, left putamen, and right putamen. Elevated RSB, as measured by the ADOS, was associated with decreased volumes in several brain regions: left thalamus, right globus pallidus, left and right putamen, right striatum and a trend for left globus pallidus and left striatum within the ASD group. These results confirm earlier reports that RSB is common early in the clinical course of ASD and, furthermore, demonstrate that such behaviors may be associated with decreased volumes of the basal ganglia and thalamus.

Introduction

Autism spectrum disorders (ASDs) are characterized by impairments in social interaction and communication, and the presence of restricted, repetitive and stereotyped patterns of behavior and interest. The repetitive and stereotyped behavior (RSB) domain encompasses a

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broad range of symptoms, including motor mannerisms, unusual preoccupations and interests, extreme rigidity and insistence on sameness. Not all individuals with a diagnosis of ASD demonstrate clear evidence of RSB and, when RSB is manifested, there may be substantial variability in the intensity and severity of symptom expression. Whether genetic contributions to RSB have a common etiology with the social and communication domains is not clear (Happe, Ronald, Plomin, 2006; Baron-Cohen & Belmonte, 2005). However, an "insistence on sameness" factor has been identified in several independent samples and genetic linkage in the 15q11-q13 region was found for families with children who scored high on this factor (Shao et al., 2003; Cuccaro et al., 2003; Szatmari et al., 2006). The variability in severity, type, and even presence or absence of RSB among individuals diagnosed with ASD lends uncertainty as to its diagnostic significance.

RSB is more often reported in individuals with ASD, as compared to those with developmental delay without autism (DD: Carcani-Rathwell, Rabe-Hasketh & Santosh, 2006; Bodfish, Symons, Parker & Lewis, 2000). Lower cognitive function increases the overall risk for RSB within ASD (Bishop, Richler & Lord, 2006; Estes, Dawson, Sterling, Munson, 2007; Richler, Bishop, Kleinke, Lord, 2007), although RSB is also commonly observed in high-functioning individuals with ASD (South, Ozonoff, McMahon, 2005). Certain subtypes of RSB, such as sensorimotor behaviors, may be more prevalent in individuals with intellectual disability (Carcani-Rathwell, Rabe-Hasketh, and Santosh (2006). RSB is not specific to ASD, as it commonly occurs in disorders including intellectual disability, obsessive-compulsive disorder, Tourettes syndrome and Parkinson's disease (Symons, Sperry, Dropik & Bodfish, 2005; Miwa, 2007).

Studies of RSB have been largely conducted with older children and adults with ASD. However, there is increasing awareness that RSB can first manifest in toddlers and preschool-aged children. Repetitive behavior is part of normal motor development in the first year of life (e.g., Thelen, 1981) and can be difficult to distinguish from RSB during this developmental period. Extremely intense interests are common and reportedly occur in one third of typically developing young children (DeLoache, Sancock, Macari, 2007). Many investigations of RSB in young children subsequently diagnosed with ASD have found no elevation in RSB at 8-30 months (Lord et al., 2006; Stone et al., 1999; Baranek, 1999; Werner, Dawson, Osterling, Dinno, 2000). In contrast, two studies have found increased parent-reported RSB and clinically observed RSB in 18-24 month old children with ASD compared to DD and typically developing (TD) controls (Richler et al., 2007; Morgan, Wetherby, Barber, 2008). Despite the complexity of assessing RSB in very young children, increased RSB appears consistently by 3-4 years of age in cohorts of children with ASD (Mooney, Gray, Tonge, 2006).

One avenue for investigating the early emergence of RSB and its role in the ASD phenotype is to distinguish its neurobiological underpinnings and early risk-factors (DiCicco-Bloom et al., 2006). Imaging studies suggest a 9-15% increase in overall brain size in preschool-aged samples of children with ASD (Courchesne et al., 2001; Hazlett et al., 2005; Sparks et al., 2002). In terms of subcortical structures within the cerebrum, basal ganglia volume has been reported to be abnormal in ASD. The basal ganglia is comprised of several distinct nuclei, generally recognized to include the putamen, caudate, and globus palidus, bilaterally. The putamen and caudate are often combined and referred to as the striatum. These structures, along with the thalami, have been implicated in RSB in individuals with ASD. The caudate has been reported to be enlarged and specifically associated with RSB among adult and adolescent samples that are higher functioning (Hollander et al., 2005; Sears et al., 1999; Voelbel et al., 2006) and in a school-aged sample (Langen et al., 2007). Thalamic volumes have been variably reported to be enlarged in school-aged samples (Herbert et al., 2003), reduced in adults (Tsatsanis et al., 2003), or, in another adult sample, equivalent to controls

but failing to show the expected linear relationship to total brain volume (Hardan, 2006). Morphometric abnormalities of the putamen and globus palidus in relationship to ASD have also been observed in school-aged samples (Herbert et al., 2003; Langen et al., 2007). We are unaware of prior reports of assessing basal ganglia or thalamic volumes, and relationships to RSB expression, in preschool-aged children with ASD. Thus, imaging studies of school-aged children, adolescents and adults suggest that the thalami and basal ganglia may play a role in manifestations of RSB in ASD. Differences in sample selection, particularly criteria regarding intellectual abilities among participants, small sample sizes and wide age-ranges may contribute to inconsistent findings in the existing literature.

In the current study, 3-4 year old children with ASD and DD were systematically assessed for RSB through clinical evaluation and parent report. A subset of these children, in conjunction with an age and sex-matched TD comparison group, underwent MRI, which allowed quantitative morphometry of the basal ganglia and thalami. Previous work demonstrated an enlargement of the cerebrum in this sample (Sparks et al., 2002). Associations between morphometric measures and repetitive behavior were assessed. We hypothesized that (1) RSB would be increased in the ASD group compared to DD controls, (2) enlargement of the basal ganglia and thalami would distinguish children with ASD from those with DD or TD, (3) basal ganglia and thalamic morphometry would be correlated with increased RSB in children with ASD.

Method

Participants

Participants were part of an NICHD longitudinal study conducted at the University of Washington and were recruited through local parent advocacy groups, community agencies, clinics, and public schools. The total clinical sample, on which RSB analyses were based, consisted of 77 children diagnosed with ASD and 34 children diagnosed with DD. All 111 children were directly assessed at age 3-4 for autism symptoms and intellectual ability as part of the longitudinal study. (Refer to the Behavioral Assessment section below for additional details on these procedures.) Clinicians made a clinical diagnosis of ASD or non-ASD, based on information obtained in the behavioral assessment following DSM-IV criteria. Children in the DD group did not meet criteria for ASD, but demonstrated delay on the measure of intellectual ability. Characteristics of children in the ASD and DD groups are described in Table 1. Family characteristics did not differ between the ASD and DD groups on maternal age at birth or SES as previously reported (Estes et al., 2009). Children in the ASD and DD groups did not differ in age or IQ (see Table 1). There are proportionally more boys in the ASD group than in the DD group (t-statistic 3.22, $p = 0.001$).

MRI evaluations were successfully obtained for a subset of this clinical sample (see Table 2). The TD group included 11 children studied at the National Institute of Mental Health (NIMH), and included in previous morphometric studies of this cohort (Sparks et al., 2002). Children in the UW TD group were included if they scored within 1 SD below or above average on the Early Learning Composite of the Mullen Scales of Early Learning (Mullen) to avoid having atypically high or low IQ. Children comprising the NIMH TD sample were recruited from the community in response to local newspaper advertisements and postings. Those children underwent 1) an evaluation process involving initial telephone screening to rule out use of medications, familial history of psychiatric illness, or special service requirements in school; and 2) an on-site physical and structured psychiatric evaluation (JNG) and neuropsychological exam to exclude children with developmental delay or psychiatric disorders. The Wechsler Intelligence Scales for Children-Revised were administered, in which all individuals in the TD group scored in the average range or above.

UW participants from all diagnostic groups had no history of serious traumatic brain injury, significant sensory or motor impairment, major physical abnormalities, neurological disease or genetic disorder associated with ASD (e.g., Fragile X). A history of seizures, prenatal or perinatal difficulties, metal implants, or use of psychoactive medications precluded participation. Exclusionary criteria were established through parent report during a telephone screening interview and examination of medical records. For the TD sample, there were no parental reports of language, social, motor, or cognitive delay; emotional or psychiatric disturbances; or special services for learning problems. Written parental/ guardian informed consent was obtained after complete discussion of the study, as approved by the University of Washington Institutional Review Board, or NIMH Institutional Review Board, for each participating child.

MRI Scans—UW imaging studies were performed on a 1.5T GE Signa Scanner using a 3-D SPGR imaging sequence (TR = 33, TE = minimum, flip angle = 30, 22-cm field of view (FOV) and 256 × 256 matrix) acquired in the coronal plane. During acquisition, a 3-mm slice thickness was reduced to 1.5-mm through zero-filling in the third phase encoding direction to improve resolution (i.e., the effective partition thickness) without loss in signal-to-noise ratio (Sparks et al., 2002). NIH studies used an identical GE scanner and acquisition parameters with the exception that coronal slice thickness was 2mm (no zero filling) at a 24-cm FOV. One of the investigators (JG) was scanned at both sites with comparable volumetric measures obtained, as described previously (Sparks et al., 2002). Children with ASD and DD were imaged during continuous intravenous infusion of propofol (Amundsen et al., 2005). TD children were scanned late at night while asleep; 8 TD children were given benadryl (25-mg PO) as they previously had experienced sedation when given this agent.

Behavioral Assessments—Behavioral evaluations of children in the ASD and DD groups were conducted by clinical psychologists or advanced doctoral students in child clinical psychology. The following measures were used to establish diagnostic group membership and assess intellectual ability and RSB.

The Mullen Scales of Early Learning: (Mullen; Mullen, 1997) was used to assess intellectual ability. The Mullen is a standardized measure for children from birth through 68 months. In addition to yielding an overall cognitive ability score, it assesses abilities in five areas: gross motor, visual reception, fine motor, receptive language, and expressive language. The gross motor scale was not obtained.

The Autism Diagnostic Observation Schedule: (ADOS; Lord, Rutter, DiLavore, Risi, 2003), RSB subscale, one of three RSB measures used in this study. This scale has demonstrated validity as a measure of RSB (Lord et al., 2006). The ADOS is an observation and play scale that provides a standardized measure used to diagnose ASDs. A series of activities are conducted to provide a variety of opportunities to observe social and communication skills and RSB. The RSB subscale was not part of the ADOS algorithm used to establish a diagnosis of ASD. Items were scored on a 3-point scale (0, no impairment or typical functioning; 1, mild impairment or possible presence of behavior; 2, definite impairment or presence of behavior) with scores of “3” rescored as “2” in accordance with guidelines (Lord et al., 2003). Behavior must occur during the ADOS assessment to be scored. Based on level of language skills, 76 participants were administered ADOS Module 1 (53 ASD, 23 DD) and 35 were administered Module 2 (24 ASD, 11 DD). Items scored on the ADOS Module 1 and Module 2 RSB subscale are “unusual sensory interests”, “hand and finger mannerisms”, and “repetitive interest/ stereotyped behavior”.

Autism Diagnostic Interview-Revised: (ADI-R; Rutter, LeCouteur, Lord, 1990), RSB subscale, was the second measure of RSB. This scale has demonstrated validity in previous studies (Lord et al., 2006). The ADI-R is a standardized parent interview used to diagnose ASDs. Parents provide examples of behavior that occur during a child's development. Items were scored on the same 3-point scale (0,1,2) as the ADOS (see above). The RSB subscale includes “circumscribed interests”, “unusual preoccupations”, “repetitive use of objects or interest in parts of objects”, “compulsions/rituals”, “unusual sensory interests”, “hand and finger mannerisms”, and “other complex mannerisms or stereotyped body movements”.

The Aberrant Behavior Checklist: (ABC; Aman & Singh, 1986) was the third measure of RSB. It is a reliable and valid 58-item measure of problem behaviors known to occur in individuals with moderate to profound developmental disability completed by the primary caregiver. Each item is scored on a scale ranging from 0 (not at all a problem) to 3 (problem is severe in degree). Scores of 3 were re-coded to 2 for comparability with the ADOS and ADI. The Stereotyped Behavior scale was used for this study. Items include “meaningless, recurring body movements”, “stereotyped behavior, abnormal, repetitive movements”, “moves or rolls head back-and-forth repetitively”, “repetitive hand, body, or head movements”, “waves or shakes the extremities repeatedly”, “rocks body back-and-forth repeatedly”.

Structural Measurements—Volumetric measurements of cerebrum, basal ganglia (putamen, caudate, globus palidus) and thalami, bilaterally, were performed by a single experienced rater blinded to diagnosis (BFS) supervised by a senior pediatric neuroradiologist (DWWS). Volumetric measurements were determined using MEASURE, a semiautomated imaging analysis program which allows simultaneous data visualization and interaction within multiple planes (coronal, axial, sagittal), consistent with prior work (Sparks et al., 2002). All measurements of the putamen, caudate, globus palidus, and thalami, bilaterally, were primarily defined in the axial view while the coronal and sagittal views were used for clarifying borders. Coronal images were reformatted into the axial plane, resulting in slices that were 0.94-mm or 0.86-mm thick (depending on FOV) for structural tracing.

Additionally, the putamen and caudate volumes on each side were combined to provide right and left striatum measurements. An example MRI in the axial view showing two-dimensional tracings of the putamen (orange), caudate (yellow), globus palidus (blue), and thalami (green), bilaterally is depicted in Figure 1. For this work, cerebral measurements were obtained using a semi-automated histogram approach to improve measurement sensitivity for small volume differences. Cerebral volume included the basal ganglia and corpus callosum and excluded the ventricles, brainstem, and cerebellum. At the level of the cerebellar peduncles, the cerebellum and brainstem were separated from the cerebrum by drawing a straight line from the most anterolateral point of the fourth ventricle to the “notch” created by the junction of the brainstem and cerebellum.

The lateral border of the caudate was defined by the anterior limb of the internal capsule and medially and superiorly by the frontal horn or body of the lateral ventricle caudal to the lateral ventricle. The antero-medial border was defined by the rostrum of the corpus callosum. Posteriorly the caudate was included to where it could no longer be clearly defined. The borders of the putamen were defined laterally by the external capsule. The putamen was defined inferiorly and medially by the internal capsule where the medial borders of the putamen were defined by the globus pallidus. The globus pallidus was defined laterally by the putamen and medially by the posterior limb of the internal capsule.

The superior border of the thalamus was established medially by the lateral ventricle and choroid plexus, anteriorly and poteriorly by the lateral ventricle and laterally by the posterior limb of the internal capsule which continues caudally to define the lateral border. Below the foramen of Monro, the medial border becomes defined by the third ventricle while the posterior-medial thalamus borders the subarachnoid space. The inferior border of the thalamus was defined by the zona incerta and its junction with the internal capsule, roughly at the level of the AC-PC line. Intra-rater reliability (B.F.S.) for volumetric measurements, using intra-class correlations based on 5 child scans, was assessed for right-sided caudate, putamen, globus palidus and thalamus (0.967, 0.980, 0.926 and 0.959, respectively).

Statistical Methods—A two-tailed, independent, two-sample t-test was used to test for differences in RSB between participants in the ASD and DD groups for each of the three RSB scales. Morphometric group comparisons were performed using the Wald Test for group differences covarying for age and gender. These comparisons were made before and after scaling for cerebral volume. Correlations between RSB scales and volumetrics were assessed using Pearson's R. Partial Pearson's R correlations were calculated to adjust for total brain volumes. Statistical analysis was performed using R version 2.10.1 statistical software.

Results

As shown in Table 3, compared with the DD group, the ASD group demonstrated significantly higher scores on all RSB scales. As shown in Table 4, increased bilateral volume of basal ganglia regions and thalami, excluding the left putamen, was observed in the ASD group relative to the DD group, when not controlling for cerebral volume. Children with ASD also showed increased volume of the basal ganglia nuclei and thalami relative to the TD group (excluding the left thalamus and left and right globus pallidus), when analyses were conducted without scaling for cerebral volume. These analyses were covaried for age and gender. However, when scaled for cerebral volume, group differences between the ASD and TD groups were no longer evident. The ASD group continued to demonstrate larger nuclei relative to the DD group even after scaling for cerebral volume, with the exception of the left striatum, left putamen, and right putamen which were no longer significantly enlarged. Examination of the mean volume by group demonstrated that statistically significant differences were due to smaller volumes of the DD group, relative to both the TD and ASD groups.

Pearsons correlations were used to assess whether RSB at age 3-4 was associated with volume of basal ganglia and thalami in the ASD group. The DD group was excluded from these analyses due to the small number of children with both structural and RSB data. The TD group was excluded because no information regarding RSB in this group was available. As shown in Table 5, increased RSB on the ADOS was associated with smaller nuclei in the case of the left thalamus, right globus pallidus, left and right putamen, and right striatum. No relationship was found with the left or right caudate or right thalamus. No significant relationships were found between ADI or ABC RSB scores and basal ganglia or thalami volume. When cerebral volume was entered as a covariate, only a trend-level relationship between the left thalamus and ABC-RSB subscale was evident.

Discussion

The current study used three well validated yet distinct measures of RSB to evaluate three related hypotheses. First, we predicted that preschool-aged children with ASD would have higher levels of RSB compared with cognitive- and age-matched children with DD. This prediction was confirmed on all measures, demonstrating that RSB symptoms are a

relatively early manifestation of ASD, observable in 3-4 year old children by both trained clinicians and parents. These findings of increased RSB in preschool-aged children with ASD compared to children with DD are consistent with some previous reports (Richler et al., 2007; Morgan, Wetherby, Barber, 2008), although not all (Cox, et al., 1995; Lord, 1995; Stone et al., 1999).

Second, we hypothesized that children with ASD would have significantly larger basal ganglia nuclei and thalami, compared to children with DD and TD. Significant enlargement of the right thalamus, left and right striatum, specifically the left and right putamen, and left and right caudate, was observed in the ASD compared to TD group. These nuclei were not significantly enlarged after scaling for cerebral volume. The DD group, in comparison to ASD group, demonstrated proportionately smaller basal ganglia and thalami regions, with a trend in this direction for the left putamen, when not scaling for cerebral volume. The DD group demonstrated disproportionately smaller bilateral thalami, striatum, caudate, and left globus pallidus, with the right globus pallidus exhibiting a trend in this direction, even after scaling for cerebral volume and controlling for age and sex. As the DD sample represents a heterogeneous clinical group, we are unable to specify a particular pathophysiologic process that might account for the decreased basal ganglia and thalamic volumes observed in these children. However, these differences do suggest that ASD may be distinguished from non-ASD developmental delays not only by clinical observation of RSB but also by brain morphometry. These findings suggest that this is not a correlate of general developmental delay but rather may reflect distinct etiological processes underlying ASD.

In our prior assessment of this sample (Sparks et al., 2002), consistent with several other studies, we found increased total cerebral volume in the children with ASD and, thus, hypothesized that these children would also exhibit enlargement of the basal ganglia and thalami. The implications and developmental trajectory of early cerebral enlargement are still largely unknown but currently under investigation through longitudinal MRI evaluation of high-risk infants having an older sibling with ASD. How best to account for cerebral enlargement when assessing volumetric differences in subcortical structures is also not clearly established. Recent imaging studies have used cerebral volume as a covariate when assessing differences between populations. This approach makes the assumption that cerebral enlargement across brain structures is a linear process and regional enlargement beyond the overall cerebral enlargement reflects specific areas implicated in the disease process. The converse assumption, that regions of the brain that are proportional to overall cerebral volume are not involved in the disease process, is also commonly held. However, these assumptions are not empirically derived. Thus, findings reflecting both “non-corrected” and “corrected” subcortical volumetric relationships to diagnosis and symptom expression are presented.

In addition to overall cerebral volume, age and developmental level need to be considered carefully. There is increasing evidence that brain structural findings in ASD vary substantially in relationship to developmental level and age. Volumetric studies of basal ganglia and thalami in ASD have primarily been conducted with older-aged samples and have generally shown enlargement proportional to overall cerebral volume with the exception of disproportionately enlarged caudate. Two previous reports on the basal ganglia in autism have included school-aged children. Increased caudate and putamen volume were reported in an ASD sample ranging from 7-14 years (Langen et al., 2007). Increased globus pallidus and putamen volumes were found in a sample aged 7 to 11 years (Herbert et al., 2003). However, prior imaging studies that assessed the relationship between ASD and the basal ganglia or thalami did not study preschool-aged children. Previous studies also have tended to include a much broader age-range than this sample. In addition, as this study employed propofol sedation, lower functioning children with ASD could be scanned. As a

result, lower functioning children comprise a substantial subset of this sample. In contrast, most previously published studies of ASD have consisted largely of individuals with higher cognitive ability. Thus, prior reported findings may not generalize to children with ASD having lower cognitive ability.

Our third hypothesis was that there would be a relationship between the volumes of specific basal ganglia and thalamic nuclei and severity of RSB in children with ASD. Surprisingly, higher levels of RSB, as measured during the diagnostic observation (ADOS), were found to be associated with *decreased* volumes of the left thalamus, right globus pallidus, right and left putamen, and right striatum when not adjusted for total cerebral volume. Observations of a relationship between smaller right striatal volumes and increased RSB presumably reflect effects of the right putamen, because a similar relationship is observed when separately evaluating the right putamen, but not the caudate. A non-significant trend for a similar relationship was found for the right thalamus. Our findings do not support earlier reports of a specific association, either positive or negative, between caudate volume and RSB symptom expression. One study of older individuals with ASD found that smaller caudate volumes were associated with higher levels of RSB (Sears et al., 1999), but this was not replicated in a subsequent study that reported increased caudate volumes were positively correlated with RSB (Hollander et al., 2005). The observed relationship between increased RSB and decreased volumes of the right globus pallidus, right and left putamen, right striatum, and left thalamus will be further assessed through longitudinal characterization of this sample. Additionally, this report focused on MRI analytic approaches that employed manual or semi-automated tracing methods to assess the basal ganglia and thalami. However McAlonan et al., 2002 utilized combined manual tracing techniques with voxel-based morphometry (VBM) and, while finding no volumetric relationships, did discern gray matter deficits by VBM for regions encompassing the basal ganglia and thalamus in young adults with Asperger syndrome. Another promising MRI analytic approach that may extend volumetric findings is the quantitative assessment of 3-D surface contour alterations, such as reported by Hwang et al., 2006 in a study of the basal ganglia in bipolar disorder. Studies utilizing other imaging analytic approaches may help clarify the functional and volumetric relationships observed in this study.

Significant relationships were not found for the two RSB scales which depended on parent report (ADI, ABC). However, these parent-report measures *were* sensitive to increased levels of RSB in children with ASD compared with DD, suggesting parents are able to reliably observe repetitive behavior in their children. The clinician-rated scale (ADOS) is based on a 45-minute observation, whereas the ADI and ABC rate behavior over the lifespan and two week period, respectively. In addition there are also qualitatively different types of RSB assessed in these measures. Perhaps these differences in time-frame and RSB types contribute to the observed method variance. These findings illustrate that further research is warranted to better understand the strengths and weaknesses of the various RSB measures currently used in autism research.

Future research on preschool-aged children with ASD may be able to distinguish “higher order” (e.g., insistence on sameness, cognitive rigidity) from “lower order” (e.g., repetitive sensory and motor behavior) RSB. Parsing RSB into distinct, meaningful, categories based on qualitative characteristics may help clarify complex relations between brain and behavior as distinct types of RSB may relate to different neuroanatomical structures and circuitry. Future research may also benefit from newer imaging analytic methods, such as 3-D topographic mapping techniques, that can provide additional structural information to that obtained from gross volumetric measurements.

Identifying the etiology of RSB in order to improve treatment approaches would be crucial for many individuals with ASD. RSB can interfere with important social and communicative learning early in development. RSB may cause impairment in daily functioning that compounds the difficulties already faced by people with ASD. By linking observed behavior to brain developmental variations we may identify risk-markers which could improve early diagnosis and prognostic accuracy. Neuroanatomical variations may also lead to refinement in our understanding of brain circuitry and the heterogeneity observed in ASD. In general, RSB associated with OCD responds to SSRIs, suggesting particular involvement of serotonergic pathways. However, RSB can also manifest in other disorders, such as Parkinson's Disease, that primarily involve dopaminergic pathways and require a different treatment strategy. Thus, a greater understanding of the neural substrates underlying RSB symptom expression in ASD will ultimately better inform intervention, both pharmacological and behavioral, that target those pathways.

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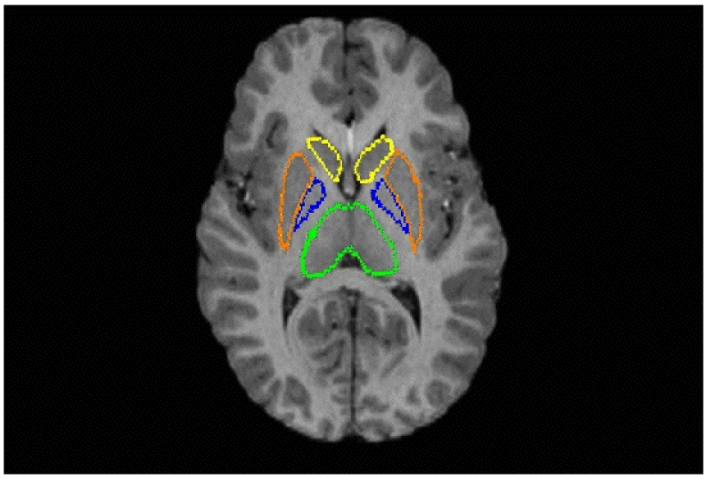

Figure 1.
MRI in the axial plane from a 3 year-old child with ASD showing tracings of caudate in yellow, putamen in orange, globus pallidus in blue and thalami in green.

Table 1
Characteristics of participants in the RSB assessment

Group	N	Gender	Months[a] (SD, range)	IQ (SD, range)
ASD	77	13f	43.6 (4.2, 34-52)	57.9 (19.7, 30-104)
DD	34	16f	44.8(5.3, 33-57)	60.7 (15.7, 29-86)

[a]Months of age at time of behavioral assessment

Table 2
Characteristics of participants in the neuroimaging procedure

Group	N	Gender	Months[a] (SD, range)	IQ (SD, range)
ASD	45	7f	47.4 (4.2, 38-54)	59.1 (20.6, 30-104)
DD	14	8f	47.5 (5.6, 40-58)	56.9 (14.4, 29-79)
TD	25	7f	47.4 (6.9, 36-56)	n/a[b]

[a] months of age at time of MRI

[b] formal testing of the TD group utilized different instruments thus mean values are not reported

Table 3

RSB scores in children with ASD versus DD

	ASD group		DD group		
RSB Scale	**M (SD)**	**N**	**M (SD)**	**N**	**T**
ADOS	2.07(1.62)	77	0.32(.73)	34	5.98**
ADI	5.42(2.34)	76	1.21(1.28)	24	8.41**
ABC	4.33(4.19)	52	0.70(1.64)	23	4.01**

** p<.001

Table 4

Volumetric comparisons among the ASD, DD, and TD groups: covaried for age and sex

	ASD n=45	DD n=14	TD n=25	ASD vs. DD[b]	ASD vs TD[b]
	Mean (SD)[a]	M(SD)[a]	M(SD)[a]	Unscaled[c] (Scaled[d])	Unscaled[c] (Scaled[d])
L Thalamus	6.77(.69)	5.58(1.44)	6.42(.49)	0.0002*** (0.008**)	0.15 (0.24)
R Thalamus	6.76(.64)	5.49(1.41)	6.25(.57)	< 0.0001*** (0.003**)	0.02* (0.90)
L Striatum	8.78(.99)	7.52(1.82)	7.93(1.04)	0.007** (0.13)	0.01* (0.41)
R Striatum	8.81(.94)	7.35(1.77)	8.02(1.07)	0.001** (0.03*)	0.01* (0.56)
L G Pallidus	1.62(.24)	1.28(.36)	1.56(.66)	0.009** (0.05*)	0.47 (0.76)
R G Pallidus	1.59(.22)	1.27(.37)	1.57(.64)	0.01* (0.08+)	0.83 (0.38)
L Putamen	4.24(.52)	3.80(.93)	3.83(.55)	0.10+ (0.79)	0.02* (0.43)
R Putamen	4.23(.49)	3.64(.85)	3.81(.54)	0.01* (0.25)	0.01* (0.40)
L Caudate	4.54(.61)	3.71(.94)	4.10(.59)	0.001** (0.02*)	0.02* (0.48)
R Caudate	4.59(.58)	3.70(1.0)	4.21(.66)	0.0006*** (0.01*)	0.05* (0.80)

[a] all volumes are reported in milliliters

[b] Wald group comparisons

[c] test for group differences without scaling for total cerebral volume

[d] test for group differences while scaling for total cerebral volume

*** <.001,

** <.01, * <.05, + <.10

Table 5

Correlations between RSB scores and basal ganglia volume in 3-4 year olds with ASD: Partial correlations with and without adjustment for total cerebral volume

	Thal		Caud		GP		Put		Stri	
	Left	**Right**	**Left**	**Right**	**Left**	**Right**	**Left**	**Right**	**Left**	**Right**
ADOS	**-.35***	**-.26**$^{+}$	-.13	-.20	-.25	**-.30***	**-.32***	**-.35***	-.25	**-.30***
TCV adj[a]	-.24	-.11	-.04	-.10	-.18	-.21	-.23	-.24	-.15	-.19
ADI	.03	.13	-.16	-.23	-.06	-.04	-.11	-.12	-.16	-.20
TCV adj[a]	.10	.24	-.14	-.20	-.03	.01	-.07	-.08	-.13	-.17
ABC	**-.32**$^{+}$	-.25	-.03	.02	-.11	.02	-.18	-.05	-.11	-.03
TCV adj[a]	**-.30**$^{+}$	-.22	.01	.04	-.08	.08	-.14	.01	-.06	.03

[a] Total cerebral volume adjusted

$^{+}$ p<.10,

* p<.05