Published in final edited form as:
Schizophr Res. 2010 October ; 123(1): 68–70. doi:10.1016/j.schres.2010.08.002.

Striatal volumes and dyskinetic movements in youth at high-risk for psychosis

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Abstract

Although dyskinesias may be one of the first behavioral indicators of progressive striatal dysfunction, a mechanism critically implicated in the pathogenesis of psychotic disorders, little is known about the association between striatal structures and abnormal movements in high-risk populations. Thirty participants with a prodromal syndrome were rated for dyskinetic movements and underwent structural magnetic resonance imaging (MRI). Volumes of striatal brain structures were delineated. Elevated hyperkinetic movements were found to be associated with smaller putamen and results were replicated in the antipsychotic naïve portion of the sample. Participants who converted over a two-year follow-up period showed significantly smaller striatal volumes and a trend towards elevated dyskinetic movements, relative to those who did not convert. Movement abnormalities may reflect a striatal pathology that is present before formal psychosis onset, and potentially reflective of a heightened vulnerability for conversion.

Keywords

Prodromal; Dyskinesia; Putamen; Caudate; Conversion; Psychosis; Striatum; Spontaneous Dyskinesia

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Contributors: Author Mittal designed the study, conducted statistical analyses and also wrote the first draft of the present manuscript. Author O'Neill aided in writing of the manuscript, data collection, and analyses. Author Bearden aided in co-directing data collection, interpreting the results, and drafting the manuscript. Author Daley aided in the writing the manuscript, obtaining primary grant funding, directing data collection, and editing the manuscript. Author Cannon aided in providing conceptualization and theory used to integrate the findings, obtaining grant funding, directing data collection, and editing the manuscript. Author Shiode helped with data collection and analyses, drafting the manuscript, and interpreting the results. All authors contributed to and have approved the final manuscript.

Conflict of Interest: Dr. Cannon is a consultant for Rules-Based Medicine on diagnostic biomarkers for mental disorders. There are no conflicts of interest to report for any of the authors.

1. Introduction

Striatal dopamine (DA) dysfunction is thought to be related to the pathophysiology of psychotic disorders (van Rossum, 1966). Within this context, individuals in the schizophrenia spectrum show spontaneous dyskinesias (e.g., writhing/flinging movements of limbs/fingers/face), independent of medication status, that are presumed to reflect a compromised cortico-striatal-pallido-thalamic circuit (Alexander, Crutcher, & DeLong, 1990). Further, evidence suggests that dyskinesias are useful in identifying those most likely to develop a psychotic disorder among youth in a high-risk clinical state (Mittal, Dhruv, Tessner, Walder, & Walker, 2007). However, no prior study has tested the hypothesized link between anatomical integrity of striatal structures and spontaneous dyskinetic movements in high-risk populations.

In this study, participants diagnosed with a prodromal syndrome (i.e., moderate levels of attenuated positive symptoms and/or decline in functioning accompanying the presence of schizotypal personality disorder and/or family history of schizophrenia) (Miller, et al., 1999) were rated for dyskinesias and evaluated with magnetic resonance imaging (MRI) and diagnostic status was followed for two-years. We hypothesized that spontaneous dyskinesias would be associated with abnormal striatal volumes, and that those participants who converted to psychosis would be distinguished by smaller structures and elevated abnormal movements at baseline.

2. Materials and Methods

2.1 Subjects

Participants in the present study were evaluated through the Center for Assessment and Prevention of Prodromal States (CAPPS), a program designed to recruit and longitudinally follow adolescents at risk for psychosis, through the adolescent risk period; please see Meyer and colleagues (2005) for a detailed description of the study. The participants in the present investigation represent those prodromal individuals from the larger CAPPS data pool that were evaluated for movement abnormalities and striatal volumes (N = 30). Exclusion criteria were the presence of a neurological/tic disorder, psychosis, mental retardation (FSIQ score < 70), substance abuse, history of significant head injury, or any MRI contra-indication. Participants underwent a screening assessment with the Structured Interview for Prodromal Symptoms (SIPS) (Miller, et al., 1999) to determine the presence of a prodromal syndrome, and individuals meeting this criteria were invited to participate in the two-year longitudinal study (see Table 1 for demographic characteristics). The Structured Clinical Interview for Axis-I DSM-IV Disorders (SCID) (First et al., 1995) was also administered to rule out a psychotic disorder (exclusion criteria) and then to assess for conversion to a psychotic disorder (e.g., schizophrenia, schizoaffective disorder, mood disorder with psychotic features) during diagnostic follow-up assessments over a two-year period.

2.2 Movement Ratings

Participants were videotaped during the structured interview at baseline while seated in a chair facing a camera behind the interviewer, and trained raters (intraclass correlation coefficients [ICCs]>.80), blind to diagnostic status, coded 45-minute segments for movement abnormalities utilizing the Dyskinesia Identification System: Condensed User Scale (DISCUS) (Kalachnik & Sprague, 1993), a valid and reliable measure of hyperkinetic movements that has been utilized in a recent investigation with a separate sample of high-risk adolescents (Mittal, et al., 2007). The sum of items 1-13 (involving the face and upper-body regions) was used to reflect the presence of dyskinesias; items 14-15 were omitted because the participants ankles/feet/toes were not visible in the videotape samples.

2.3 Imaging

A magnetization prepared gradient echo (TR/TE = 1.9s/4.38 ms, matrix = 256×256, FOV = 256mm×256mm, 1 mm slice thickness, 160 slices with no gap) whole-brain structural MRI scan was acquired from each participant on a 1.5-T Siemens Sonata scanner at baseline. Target subcortical nuclei were delineated automatically on MRI using the FMRIB's Integrated Registration and Segmentation Tool (FIRST) algorithm within the FMRIB's Software Library (FSL) image-processing suite (Patenaude, 2007). FIRST also returned values for each participant's total intracranial volume (TICV) (i.e., the sum of whole-brain grey matter +white matter+cerebrospinal fluid), and each structure was divided by the TICV to control for whole brain volume.

2.4 Data analysis

Kolmogorov-Smirnov tests revealed that distributions of structural and dyskinesia variables met the assumptions for parametric statistics. Two partial correlations, controlling for age, gender, and prescription of psychotropic medications (i.e., stimulant, antidepressant, antipsychotic) were conducted to examine the relationship between the volumes for putamen and caudate and dyskinetic movements. Analysis of Covariance (ANCOVA), controlling for age, gender, and prescription of psychotropic medications (i.e., stimulant, antidepressant, antipsychotic), were used to examine group differences in striatal structures between those participants who did and did not convert to a psychotic disorder during the 2-year diagnostic follow-up period. ANCOVA analyses controlling for classes of medication were also used to examine group differences in spontaneous movements between those participants who did and did not convert.

3. Results

3.1 Associations between spontaneous dyskinesia and striatal volumes

As predicted, there was a moderate negative relationship between dyskinesias and putamen volume ($r = -.37$, $p \leq .05$) but not caudate volume ($r = -.04$, $p = .42$). Previous MRI studies have noted that antipsychotic medications can have marked effects on basal ganglia volumes (Taylor, Christensen, Holcomb, & Garver, 2005). To address this issue beyond a medication covariate strategy, analyses were repeated omitting the patients in treatment with antipsychotic medications (n = 6) and the results did not change in direction or magnitude (putamen: $r = -.39$, $p \leq .05$; caudate: $r = -.07$, $p = .38$).

3.2 Conversion

A total of 5 (16.6%) of the prodromal participants converted to a psychotic disorder during the two-year follow up period [Age: mean = 14.57, SD = 3.33; Gender: males = 4, female = 1; Diagnosis: schizophrenia =1, schizoaffective disorder = 3, depression with psychotic features = 1]. In supplementary analyses, ANCOVAs controlling for age, gender, and classes of medication were conducted to examine differences in putamen and caudate volumes and spontaneous movement abnormalities between those participants who converted and did not convert. Results showed significant group differences [$F(1,28) = 3.01$, $p \leq .05$, $\eta^2 = .45$], indicating that those participants who converted (mean = 5.51 cm^3; SD = .4) had smaller baseline putamen volumes than those who did not (mean = 5.83 cm^3; SD = .5). Furthermore, results indicated significant group differences for caudate volumes [$F(1,28) = 4.55$, $p \leq .01$, $\eta^2 = .55$]; participants who converted (mean = 3.74 cm^3; SD = .6) had smaller caudate volumes than those who did not (mean = 3.99 cm^3; SD = .4). Consistent with findings in a distinct prodromal sample (Mittal & Walker, 2007), ANCOVA analyses also indicated a trend toward increased spontaneous movement abnormalities at baseline in the converted group (mean = 8.80; SD = 2.77) when compared with the non-converted group (mean = 7.62; SD = 6.35; F

(1,28) = 1.38, p = .14). It is important to note that this conversion rate is a simple percentage, and that the conversion rate in the larger CAPPS sample from which this subset of participants was drawn is on the order of 40% (using a Kaplan-Meier survival analysis, which accounts for censoring).

4. Discussion

Findings suggest that elevated rates of dyskinesias are associated with smaller putamen, but not caudate volumes. This is consistent with a study of patients with schizophrenia observing that neurological soft signs (including motor and sensory integration deficits) were associated with reduced grey matter volume in the putamen (Dazzan, et al., 2004). The present findings are also in-line with a theory that the putamen is primarily a motor and the caudate a cognitive nucleus (Grahn, Parkinson, & Owen, 2008); however, the present sample size does not yield sufficient power to definitively support a null hypothesis in this regard.

Present findings are particularly noteworthy as they indicate that spontaneous dyskinetic movements may indeed reflect abnormalities in the dorsal striatum, and that this dysfunction appears to be present prior to the onset of psychosis and is not the direct byproduct of antipsychotics. Findings that smaller baseline caudate and putamen volumes distinguished those prodromal participants who eventually went on to convert to overt psychosis during the two-year follow-up period also suggest that basal ganglia dysfunction occurs early in the pathogenesis of psychosis, and taken together these results show promise for the notion that markers of frontal-subcortical vulnerability can be useful in efforts for early identification and treatment. This view is also consistent with an in vivo [^{18}F]6-fluoro-l-dopa positron emission tomography (PET) study, observing that elevated striatal DA uptake predates the onset of schizophrenia in high-risk individuals (Howes, et al., 2009).

This preliminary study is limited by the lack of a control group and data for the feet/ankles/toes. However, it should be noted that previous studies examining movement abnormalities have noted no significant differences between high-risk youth and healthy controls in this region (Mittal, et al., 2007). It is also important to consider that the supplementary analyses examining group differences between converting and non-converting participants included a very small number of converters, and the results should be interpreted with caution and future studies with larger samples of converted participants are necessary for replication. Results invite future studies, including investigation of receptor abnormalities and regional functional or resting-state activation possibly associated with dyskinesias in psychosis.

Acknowledgments

Role of the Funding Source: This research was supported by National Institutes of Health Grants MH65079 to TDC, Grants MH14584-33 and MH087258-01to VM and a NARSAD 2010 Young Investigator grant to MD. Support was also provided by NIMH P50 MH066286 awarded to KN. NIMH and NARSAD had no further role in study design; in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication.

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Table 1

Demographics of High-risk Participants (N=30)

Characteristics	
Gender	
Males	22(72.3%)
Females	8(26.7%)
Total	30
Age: Mean/SD	17.2(2.9)
Medication	
Anti-psychotics	5(16.7%)
Stimulants	3(10.7%)
Antidepressants	16(53.3%)
Striatal Volumes: Mean(SD) [a]	
Putamen	5.8(0.5)
Caudate Nucleus	3.9(0.4)
Total Intracranial Volume[b]	1422.3(127.7)
Movement Abnormality: Mean(SD) [c]	8.0(5.8)

[a] Uncorrected volumes, expressed in cm^3;

[b] Sum of grey and white matter and cerebral spinal fluid in cm^3;

[c] Sum of items 1-13 on the Dyskinesia Identification System: Condensed User Scale (DISCUS).