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Research report

Anatomic brain magnetic resonance imaging of the basal ganglia in pediatric bipolar disorder ☆

Mary S. Ahn, Janis L. Breeze, Nikos Makris, David N. Kennedy, Steven M. Hodge, Martha R. Herbert, Larry J. Seidman, Joseph Biederman, Verne S. Caviness, Jean A. Frazier *

Cambridge Health Alliance Department of Psychiatry 1493 Cambridge St. Cambridge, MA 02139, USA

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Abstract

Background: Basal ganglia (BG) enlargement has been found in studies of adults with bipolar disorder (BPD), while the few studies of BPD youths have had mixed findings. The BG (caudate, putamen, globus pallidus, nucleus accumbens) is interconnected with limbic and prefrontal cortical structures and therefore may be implicated in BPD.
Methods: Sixty-eight youths (46 with BPD, 22 healthy controls) received neurological and psychiatric assessment, semi-structured interviews, and neuropsychological testing, followed by anatomic magnetic resonance imaging on a 1.5 Tesla scanner. After image segmentation, log BG volumes and asymmetry indices were analyzed using MANOVAs controlling for the effects of cerebral volume, age, sex, and diagnosis. These omnibus tests were followed by univariate linear regression models of each BG structure.
Results: Youths with BPD had a trend for larger right nucleus accumbens (NA) volumes ($p = 0.089$). There were no significant group asymmetry differences, nor volume differences in the caudate, putamen, and globus pallidus. When analyzed separately by pubertal status, the prepubertal group had significantly larger total NA ($p = 0.035$) versus healthy controls, while the pubertal group did not show significant differences in the NA versus healthy controls.
Limitations: The size of the control group is relatively small, possibly limiting our power to detect significant group differences. The inter-rater reliability for the NA is not as strong as the other structures; the finding of volume differences in this structure is preliminary and warrants replication.
Conclusions: Youths with BPD had larger right NA volumes; this enlargement was most pronounced in the prepubertal group. The differences between these findings and those seen in adult BPD imply a neurodevelopmental phenomenon.

Keywords: Pediatric bipolar disorder; Neuroimaging; Basal ganglia; Caudate; Putamen; Globus pallidus; Nucleus accumbens; Magnetic resonance imaging (MRI)

☆ Contributors: Dr. Frazier designed the study and wrote the protocol, with the assistance of Drs. Biederman, Caviness, Seidman, and Herbert. Drs. Frazier and Ahn recruited and characterized the patients in the study. Drs. Kennedy and Makris created the neuroanatomic tools used in this project and oversaw all image segmentation and analysis. Dr. Ahn, Ms. Breeze, and Mr. Hodge undertook the statistical analyses, and Drs. Frazier, Makris, Kennedy, and Ahn wrote substantial portions of the manuscript. All authors contributed to and have approved the final manuscript.Role of funding source: Funding for this study was provided by NIMH K08 MH01573 to JAF. The NIMH 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.
* Corresponding author. Tel.: +1 781 306 8631; fax: +1 781 306 8644.
E-mail address: jfrazier@challiance.org (J.A. Frazier).

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1. Introduction

Neuroanatomic models of bipolar disorder (BPD) propose that the basal ganglia (BG) structures (e.g., the caudate, putamen, nucleus accumbens, and globus pallidus) are involved in affective regulation (Soares and Mann, 1997; Phillips et al., 2003a,b). Neuroimaging approaches to the study of pediatric BPD, in particular, represent a promising field of research for elucidating the developmental course of putative neural abnormalities. To date, the magnetic resonance imaging studies that have been done in adults with BPD have yielded conflicting findings regarding BG volumetric abnormalities. Some adult studies report larger BG (Aylward et al., 1994; Strakowski et al., 1999, 2002) and others report no significant differences from healthy controls (Strakowski et al., 1993; Swayze et al., 1992; Brambilla et al., 2001). There have been four published studies examining BG volumes in children and adolescents with BPD (DelBello et al., 2004; Wilke et al., 2004; Dickstein et al., 2005; Sanches et al., 2005b). One study reported significantly smaller left nucleus accumbens in BPD youths (Dickstein et al., 2005). Two of the studies in youths with BPD failed to find differences in striatal volumes (Dickstein et al., 2005; Sanches et al., 2005a) while the other two studies found larger striatal volumes (DelBello et al., 2004; Wilke et al., 2004). However, the prior studies done in children include a relatively modest numbers of patients. Clearly, more studies with larger sample sizes of children with BPD are necessary to understand the involvement of the BG in pediatric BPD.

We therefore conducted an MRI study of pediatric BPD to evaluate the basal ganglia using magnetic resonance imaging. Our *a priori* hypothesis, based on studies of youths affected by the illness, was that the BPD group would have a smaller nucleus accumbens (NA) and larger striatal volumes compared to the healthy control group.

2. Methods

The protocol was approved by the McLean Hospital Institutional Review Board. All subjects signed assent forms and their parents/legal guardians signed consent forms.

2.1. Subjects

Patients aged 6–16 years, who had a DSM-IV diagnosis of bipolar I disorder-lifetime were recruited through the McLean Hospital outpatient program and through advocacy groups. Healthy controls, with no DSM-IV Axis I diagnosis based on semi-structured and clinical interviews, were recruited through local advertisements. The exclusion criteria in both groups were: presence of major sensorimotor handicaps; full-scale IQ < 70; presence of learning disabilities; history of claustrophobia, autism, schizophrenia, anorexia or bulimia nervosa, alcohol or drug dependence or abuse (in the 2 months prior to the scan or total past history of 12 months or greater); active medical or neurological disease; presence of metal fragments or implants; history of electroconvulsive therapy; and current pregnancy or lactation.

All children, including the healthy controls, underwent diagnostic semi-structured (Kiddie Schedule for Affective and Schizophrenic Disorders: Epidemiologic Version-KSADS-E) (Orvaschel and Puig-Antich, 1987) and clinical interviews by board-certified child psychiatrists. Additionally, parents were administered an indirect KSADS-E regarding their children by trained raters (see Frazier et al., 2005 for more detail). All raters achieved a high degree of inter-rater reliability; the mean kappa was 0.9 and all disorders achieved kappa coefficients of > 0.82. The measures of psychopathology were obtained using the Young Mania Rating Scale (YMRS) (Young et al., 1978) and past and current Global Assessment of Functioning (GAF) (APA, 1994).

2.2. Drug exposure

Antipsychotic doses were converted to chlorpromazine equivalents and this variable, as well as the total number of medications at the time of scanning, were used in correlational analyses with the BG volumes where there was a significant difference between groups.

2.3. Pubertal status

In an exploratory analysis to assess the association of volumetric differences relative to pubertal status, BPD and healthy control samples were divided into prepubertal and pubertal groups. The prepubertal group consisted of youths in Tanner Stage I. The pubertal group consisted of youths in Tanner Stages II–V (Tanner, 1962).

2.4. MRI protocol

Images were acquired at the McLean Hospital on a 1.5 Tesla General Electric Signa Scanner. Acquisitions included a T1-weighted sagittal scout series, coronal T2-weighted sequence to rule out gross pathology, and coronal volumetric T1-weighted spoiled gradient echo-imaging sequence (prep = 300 ms, TE = 1 min, flip angle 25°, FOV = 30 cm and 24 cm, slice thickness = 1.5 mm, acquisition matrix = 256 × 192, number of excitations = 1