A Preliminary Investigation of Corpus Callosum and Anterior Commissure Aberrations in Aggressive Youth with Bipolar Disorders

Kirti Saxena, M.D.,¹ Leanne Tamm, Ph.D.,² Annie Walley, M.S.W.,³ Alex Simmons, B.A.,³
Nancy Rollins, M.D.,⁴ Jonathan Chia, M.S.,⁵ Jair C. Soares, M.D.,¹
Graham J. Emslie, M.D.,³ Xin Fan, Ph.D.,^{6,7} and Hao Huang, Ph.D.^{4,7}

Abstract

Objective: Although behavioral deficits in bipolar disorder (BPD) are well described, the specific brain white matter (WM) disruptions have not been completely characterized, and neural mechanisms underlying dysfunction in BPD are not well established, particularly for youth with BPD and aggression. This preliminary study utilized diffusion tensor imaging (DTI) to investigate commissural tracts (corpus callosum [CC] and anterior commissure [AC]) in youth with BPD, because disruption of interhemispheric communication may contribute to the emotional deficits that are characteristic of the illness.

Method: DTI was used to investigate WM in 10 youth (7–17 years of age) with BPD and 10 typically developing age-matched controls. Tract-based spatial statistics voxel-wise analysis was used to compare fractional anisotropy (FA) of the two groups. We specifically focused on five subdivisions of the midsagittal CC as well as on the decussation of AC, which connects the temporal lobes. Exploratory correlations between FA values and life history of aggression scores were calculated for the BPD group.

Results: Youth with BPD had significantly lower FA values in the callosal genu and AC. FA values in the AC were negatively correlated with a life history of aggression in the BPD group.

Conclusions: These results contribute to a growing literature implicating a role for the genu of the CC in BPD and are the first to report WM variations in the AC of children with BPD. Taken together with the correlational data for aggression and the role of the AC in emotional processing, our data provide preliminary evidence for a possible association between the structural integrity of the WM of the AC and aggression in pediatric BPD.

Introduction

BIPOLAR DISORDER (BPD) is a serious, chronic illness associated with aggressive behavior, suicidality, and high risk, all of which are known to decrease quality of life (Doerfler et al. 2010). Onset of BPD in childhood tends to be more severe and complicated than BPD of adult onset (Carter et al. 2004; Perlis et al. 2004). The National Institute of Mental Health's Systematic Treatment Enhancement Program for BPD study included 983 subjects (Perlis et al. 2004). Of those subjects in whom the age of onset of mood symptoms could be determined, 27.7% had age of onset before age 13. Early onset was associated with higher rates of co-morbid anxiety disorders and substance abuse, more recurrences, shorter periods of euthymia, and a greater likelihood of suicide attempts and violence (Perlis et al. 2004).

The neural basis of BPD is not well understood. In recent years, it has been recognized that white matter (WM) makes an important contribution to cognition and emotion. WM comprises nearly half the brain volume and plays a key role in development, aging, and many neurological and psychiatric disorders across the life span (Filley 2005). Thus, investigating WM may elucidate our understanding of psychopathology in BPD.

Diffusion tensor imaging (DTI) provides information about WM microstructure *in vivo* (Basser et al. 1994; Huppi et al. 2001), and permits the study of connections among anatomically and functionally defined brain regions (Conturo et al. 1999). Myelin sheaths and cell membranes restrict the diffusion of water perpendicular to the direction of the axons in WM, whereas water diffuses relatively freely parallel to the axons. This directional dependence of diffusion is often quantified as anisotropy, which reflects myelination of

¹Department of Psychiatry, University of Texas Health Science Center at Houston, Houston, Texas.

²Division of Behavioral Medicine and Clinical Psychology, Cincinnati Children's Hospital, Cincinnati, Ohio.

Departments of ³Psychiatry and ⁴Radiology, University of Texas Southwestern Medical Center, Dallas, Texas.

⁵Philips Healthcare, Cleveland, Ohio.

⁶School of Software, Dalian University of Technology, Dalian, China.

⁷Advanced Imaging Research Center, University of Texas Southwestern Medical Center, Dallas, Texas.

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axons and the coherence of axonal orientation (Neil et al. 1998). Fractional anisotropy (FA) is a unit-less and normalized measure of diffusion anisotropy (ranging from 0 to 1) that provides information about the degree of fiber organization and integrity. Mean diffusivity that characterizes the size of the measured diffusion tensor has also been used to detect WM abnormality. Diminished anisotropy of water diffusion and increased apparent diffusion coefficient (ADC) has been proposed to reflect compromised WM integrity (i.e., a disruption or disorganization of tracts) (Beaulieu 2002). WM has an extremely high level of structural organization that compartmentalizes and restricts water motion; thus, DTI, which is inherently sensitive to water diffusivity, has great potential for investigating WM contributions to psychopathology, including BPD.

A recent review suggested that the corpus callosum (CC) may play a role in the pathogenesis of BPD (Bellani et al. 2009). The CC is involved in integrating sensory-motor functions, attention, language, and memory-executive functions frequently compromised in BPD. The CC is, by far, the largest WM structure in the human brain, and the midsagittal CC can be further partitioned into segments connecting different parts of the two cerebral hemispheres (Fig. 1a) (Huang et al. 2005). Few detailed analyses at the multiple segments of the CC have been conducted for children and adolescents with BPD, which is somewhat surprising given that investigating these segments may reveal which brain areas are affected by the CC disruption. For example, the genu connects the prefrontal and orbital areas, and the splenium of CC connects the occipital areas. DTI studies of the CC in children and adolescents with BPD report lower FA values in the genu and body (Frazier et al. 2007), higher ADC and reduced fiber coherence in the splenium (Pavuluri et al. 2009), and lower FA values throughout the CC (Barnea-Goraly et al. 2009). It has been suggested that maldevelopment of the CC and potential impaired communication between hemispheres may affect brain maturation in pediatric BPD (Bellani et al. 2009).

To our knowledge, no DTI studies have reported findings in the anterior commissure (AC), a relatively small tract connecting the temporal lobes and amygdala of both hemispheres (the AC connects the middle and inferior temporal gyri) (Fig. 1b) in BPD. The size of the AC has been postulated to play a role in emotional intelligence and social sensitivity (Clark et al. 2010). Since individuals with BPD have deficits in both emotional and social functioning, our exploratory hypothesis is that the AC may play a

role in the presentation of the disorder. The lack of reported alterations in the tensor metrics of the AC to date may be related to the small size of this structure and the low inherent resolution of DTI used in clinical practice.

In our preliminary study, we acquired high-resolution DTI scans from 10 youth with BPD and compared the DTI data with that of 10 age-matched healthy control subjects collected as a part of another research study (Rollins et al. 2009). We focused on the commissural tracts, as the studies to date reporting disruption of interhemispheric communication in BPD may be related to the emotional deficits characteristic of the illness. We specifically compared FA values between groups for five segments of the CC and the AC. We hypothesized that there would be decreased FA in the CC for the group with BPD. We did not have a specific directional hypothesis for the AC, as no previous studies have reported DTI findings in this region for individuals with BPD, although we anticipated WM abnormalities in that region. In addition, *post hoc* correlations between DTI scalars and scores on a measure of aggression were performed for the participants with BPD to explore the relationship between the structural aberration and behavior.

Methods

This study protocol was approved by the University of Texas Southwestern Medical Center Institutional Review Board. Oral and written informed consent was obtained from parents, and oral and written assent was obtained from participants before initiating any study procedure.

Participants with BPD

Ten youth (ages 7 to 17 years inclusive—mean age 13.9 ± 3.6 ; 60% female) with pediatric BPD were recruited from the Pediatric Bipolar Disorders Outpatient Specialty Clinic at Children's Medical Center in Dallas. We opted to allow inclusion of participants more broadly with bipolar spectrum disorders (BPD type I, BPD type II, and BPD not otherwise specified [NOS]). Many children and adolescents in the community do not fit the classic *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition (DSM-IV) (American Psychiatric Association 1994) criteria for BPD type I and may be diagnosed as having BPD NOS (Lewinsohn et al. 1995). In outpatient clinical settings, this ends up being, by far, the most common presentation. The Course and Outcome of Bipolar Youth (COBY) study describes a phenotypic presentation of

FIG. 1. Three-dimensional demonstration of corpus callosum (CC) (a) and anterior commissure (AC) (b). In panel (a), blue, green, orange, yellow, cyan, and red color indicate the CC fibers connecting to orbital, frontal, parietal, occipital, temporal lobe, and subcortical nuclei, respectively. In panel (b), red color indicates the AC fibers connecting to the temporal lobe and orbitofrontal lobe. A color version of this figure can be found in the online article at www.liebertpub.com/cap.

children and adolescents with BPD type II and BPD NOS that is on a continuum with that of youth with BPD type I (Axelson et al. 2006). Indeed, the COBY study reported that over a 4-year period, 25% of youth with BPD type II converted to BPD type I, and 38% of those with BPD NOS converted to BPD type I or BPD type II (Birmaher and Axelson 2006).

Participants were evaluated by using the Schedule for Affective Disorders and Schizophrenia for School-aged Children-Present and Lifetime Versions (K-SADS-PL) (Kaufman et al. 1997) to assess clinical diagnoses. We utilized criteria from the COBY study to establish the diagnosis of BPD NOS (Axelson et al. 2006; Birmaher and Axelson 2006). Symptom severity was assessed by using the Young Mania Rating Scale (Young et al. 1978) for current manic symptoms, the Quick Inventory of Depressive Symptoms—clinician rated and adolescent self-report (Rush et al. 2003; Trivedi et al. 2004) for current depressive symptoms, the Clinical Global Improvement-Severity (Leon et al. 1993) scale for global severity, and the Life History of Aggression scale (Coccaro et al. 1997) for aggression. Next, we provide additional information on this lesser known scale.

The Life History of Aggression scale is a clinician-administered semi-structured interview. The scale assesses several domains including temper tantrums, physical fighting, verbal fighting, specific assaults on other people, specific assaults on property, specific assaults on self, suicide attempts, school disciplinary problems, problems with supervisors at work, antisocial behavior not involving police, and antisocial behavior involving police. The range of scores for each item is from 0 to 5 (0 = no events; 5 = “so many events that they cannot be counted”). The maximum possible score is 55, and total scores greater than 15 can be indicative of high life time aggressive behaviors (Coccaro et al. 1997). The Life History of Aggression scale has been shown to have excellent test-retest stability, inter-rater agreement, and internal consistency reliability (Coccaro et al. 1997).

All evaluations were performed by a trained masters-level research assistant and confirmed by a board-certified child and adolescent psychiatrist (K.S.). Inter-rater reliability on the psychometric instruments was established by rating video-taped interviews, observing interviews conducted by trained raters, and performing interviews while being observed by a trained rater.

All participants in the BPD group had a confirmed diagnosis of BPD type I or BPD NOS. Participants were excluded for history of claustrophobia, autism, schizophrenia, anorexia or bulimia nervosa, current pregnancy or lactation and metal implants, history of alcohol or substance use within the preceding 3 months before the scan, neurological disorder, and a history of head trauma that resulted in loss of consciousness lasting for more than 10 minutes. Table 1 provides the clinical characteristics for the BPD group.

Participants with BPD were scanned at the Advanced Imaging Research Center at the University of Texas Southwestern Medical Center by using a 3T Philips Achieva MR system. All were outpatients and on psychotropic medication at the time of scanning.

Healthy controls

Data from 10 healthy controls (mean age 13.6 ± 3.6 ; 40% female) obtained in the context of a different DTI study were utilized (Rollins et al. 2009). The controls had no lifetime history of any psychiatric disorder based on clinical interview with the participant and parent(s). The healthy controls were scanned at the Children’s Medical Center of Dallas imaging facilities on a 3T Philips Achieva MR system using the same scanning protocols.

TABLE 1. CLINICAL CHARACTERISTICS OF THE BIPOLAR DISORDERS GROUP (N = 10)

Primary diagnosis	BPD type I: 8 BPD NOS: 2
Co-morbid diagnoses	Attention-deficit/hyperactivity disorder: 5 Oppositional defiant disorder: 1 Anxiety disorder, NOS: 2
Age of onset of bipolar disorder	9.6 years $\pm$ 3.1 years
Age when first medicated	9.0 years $\pm$ 3.9 years
Mood state at time of scan	Manic: 1 Mixed: 1 Depressed: 1 Euthymic: 7
Medications at time of scan	Lamictal: 7 Lithium: 6 Trileptal: 2 Atypical antipsychotics: 6 SSRI: 2 Trazodone: 3 Stimulant: 4 Strattera: 1
Life history of aggression total score	24.8 $\pm$ 4.5

BPD = bipolar disorder; NOS = not otherwise specified; SSRI = selective serotonin re-uptake inhibitors.

DTI protocol

In vivo human DTI data were acquired by using a single-shot echo-planar imaging sequence with SENSE parallel imaging scheme (SENSEitivity Encoding, reduction factor = 2.5). The imaging matrix was 112×112 with a field of view of 224×224 mm (nominal resolution of 2 mm), which was zero filled to 256×256 . 2 mm thick slices were acquired parallel to the anterior-posterior commissure line (AC-PC). A total of 60 to 65 slices covered the entire hemisphere and brainstem without gap. Slice number was determined by the height of the participant’s brain. The echo time and repetition time were 97 milliseconds and 7.78 seconds without cardiac gating. The diffusion weighting was encoded along 30 independent orientations (Jones et al. 1999) and b value, which indicates amount of diffusion weighting, was 700 s/mm^2 (Dubois et al. 2008; Tamnes et al. 2010). Three additional images with minimal diffusion weighting were acquired. Imaging time for each sequence was 4 minutes and 15 seconds. To increase signal to noise ratio (SNR), three repetitions were performed, thus resulting in a total imaging time of 13 minutes. The tensor fitting protocol is identical to that used in our previous study (Huang et al. 2011).

Between scanner comparison

Although both groups were scanned in the same type of scanner (Philips Achieva 3T) using the same scanning protocol, we were concerned that significant results might be resulting from scanner differences rather than true group differences. Thus, we conducted a quality assessment comparing data from the two scanners. A healthy volunteer was scanned on the same day in both scanners using the identical imaging protocol as in this study. We then compared the FA profile for the whole brain and several regions of interest including the genu of midsagittal CC, splenium of midsagittal CC, and cerebral peduncle (CP) in the axial plane of decussation of superior cerebellar peduncle. The differences in FA values were negligible and less than 1.5% across brain regions, thus

indicating comparability of the DTI data acquired from the two scanners.

Voxel-wise statistical analysis

Tract-based spatial statistics (TBSS) from the FMRIB software library (FSL, www.fmrib.ox.ac.uk/fsl) was used for voxel-wise comparison (Smith et al. 2006). This voxel-wise method compared the FA values of each group at core or skeletons of the WM to effectively alleviate partial volume effects. With TBSS pipeline, FA data of all participants were aligned into a common space (a control subject with median brain size) by using a non-linear registration algorithm. The mean FA image was created and thinned to generate a mean FA skeleton that represented the core of all tracts common to the group. The threshold was adjusted to $FA > 0.2$ to include the major WM pathways but excluded peripheral tracts where there was significant intersubject variability and partial volume effects with gray matter. Each participant's aligned FA data were projected into this skeleton, and the resulting data were fed into voxel-wise cross-subject statistics.

Comparison of FA values of AC and CC

The comparisons of FA values of AC and CC were performed in the MNI152 template space. In the midsagittal slice, CC was evenly segmented into five compartments along the anterior-to-posterior axis from its most anterior to most posterior boundary (genu and splenium correspond to segment 1 and 5, respectively). FA values at the skeleton voxels of each segment were averaged to represent the CC integrity of this segment. At the axial plane of AC decussation, a box of 15 voxels by 15 voxels, which includes the significant cluster at midsagittal AC, from TBSS analysis was placed. The FA values of skeleton voxels inside this box were averaged for each subject to represent AC integrity. A student t-test was then

conducted to compare the integrity of CC segments and AC from the BPD and control groups.

To ensure that the big red clusters in AC and anterior CC (pointed by arrows in Fig. 2) are not spurious false positive outcomes, small-volume FDR correction (Versace et al. 2008; Cullen et al. 2010) was applied. These small volumes were anatomically defined regional masks (highlighted as bright regions in Fig. 2) containing skeleton voxels 100 times larger than the red clusters at AC or anterior region of CC. The FSL statistical tool was used for multiple-comparison correction of the small volume.

Correlation of FA values in CC and AC with life history of aggression for participants with BPD

We performed correlations with the Life History of Aggression scores to assess whether differences in FA values within regions of significant differences between groups were associated with aggressive symptomatology. Spearman's rho correlations (two-tailed) were performed by correlating FA values in the CC (genu) and AC with the total Life History of Aggression score.

Results

We observed statistically significant differences for FA values at CC and AC between the BPD and healthy control participants (Fig. 3). Specifically, as shown in the right panel of Figure 2, the group with BPD had significantly lower FA values in the anterior region of the CC (uncorrected $p < 0.001$), but no statistically significant group differences were observed in the middle and posterior CC. Significant group differences were observed in the AC (left panel of Fig. 2), with the BPD group having lower FA values (uncorrected $p < 0.001$). The FA differences at the two clusters of AC and anterior region of CC (indicated by the arrows in Fig. 2) are significant even after small volume corrections (corrected $p < 0.05$).

FIG. 2. Group analysis results from tract-based spatial statistics. The arrows in both left and right panels point to the clusters of significantly lower fractional anisotropy (FA) in the anterior commissure (AC) (left) and anterior corpus callosum (CC) (right). The small volumes used for multiple comparison corrections of the clusters are bright regions highlighted in both panels. The right panel also shows the segmentation of the CC into five compartments. A color version of this figure can be found in the online article at www.liebertpub.com/cap.

FIG. 3. Group comparisons of FA at each segment of midsagittal CC and decussation of AC. Asterisk indicates significant differences (uncorrected $p < 0.001$). FA = fractional anisotropy; CC = corpus callosum; AC = anterior commissure.

Results from our exploratory correlational analyses in the BPD group were also significant for the AC (Fig. 4). Specifically, we observed a significant negative correlation between FA values in the AC and life history of aggression (AC, $r = -0.66$, $p = 0.04$). The correlation between CC and life history of aggression was in the same direction but not significant (CC segment 1, $\rho = -0.42$, $p = 0.23$).

Discussion

These results add to a growing body of literature implicating a role for abnormalities in the CC in youth with BPD. What is different about our preliminary study is that we have included youth with bipolar spectrum disorders with aggression, whereas other DTI studies have reported only on youth with BPD type I and did not report rates of aggression. Our results also suggest a role for WM disruptions in the AC for youth with BPD, which appear to be associated with aggression.

The findings of lower FA values in the genu of the CC for the group with BPD are remarkably consistent with those reported by Barnea-Goraly et al. (2009), who also utilized TBSS. Further, structural studies report reduced volumes specifically in the genu of the CC in BPD (Brambilla et al. 2009). The anterior component of the CC provides interhemispheric connections between the left

and right prefrontal cortices thought to integrate hemispheric functioning and to play a key role in the integration of emotional and cognitive information (Womer et al. 2009).

Compromised WM integrity in the AC has not been previously reported, possibly due to challenges achieving sufficient resolution with DTI protocols used in clinical practice. However, the abnormalities we observed in the AC are prominent and statistically significant. Further, inspection of all FA maps in their native spaces suggests that the findings are not due to misregistration. The AC connects the temporal lobes and amygdala of both hemispheres. Since the amygdala plays a role in the mediation of emotional processing in BPD (LeDoux 2000), and volumetric deficits in the amygdala of youth with BPD have been documented (Chen et al. 2004; DelBello et al. 2004; Blumberg et al. 2005; Chang et al. 2005; Dickstein et al. 2005), our exploratory finding of decreased FA in the AC may contribute additional information about the pathophysiology of this illness in children and adolescents.

The fact that AC abnormalities were found to play a role in BPD and correlated with aggression is particularly interesting. To our knowledge, no DTI studies have investigated WM integrity in aggressive youth with bipolar spectrum disorders, a clinically significant group to study as lifetime aggression has been associated with risk for suicidality (Grunebaum et al. 2006). Further, aggressive bipolar youth commonly present to child psychiatric clinics,

FIG. 4. Spearman correlations of FA values in the genu of the CC and AC with life history of aggression total score in the bipolar disorders group. FA = fractional anisotropy; CC = corpus callosum; AC = anterior commissure.

as their aggression cannot be managed by their primary caretakers, and they appear to be less responsive to treatment (Jensen et al. 2007). The results of our exploratory analyses showing that reduced FA values in the AC were significantly negatively correlated with the Life History of Aggression scores, even in such a small sample, suggest the possibility of an association between the structural integrity of the WM of callosal connections and aggression in youth with BPD. Future studies looking at bipolar youth with aggression with a larger sample will be needed for further examination of potential tract specific impairments in youth with bipolar spectrum disorders and aggression.

It should be noted that there are some potential limitations to this preliminary study which make replication imperative. Although our sample size did provide enough power to detect group differences, the sample size is still limited and may have restricted us from finding disruption in other WM regions where FA changes are relatively smaller but may still be significant given a larger sample. In addition, the completely new findings on the significantly decreased FA values in the AC and the significant correlation between FA in the AC and Life History of Aggression scores were not hypothesized. Other potential limitations relate to the BPD sample that included youth with BP Type I and BP NOS, who were all taking psychotropic medications, and evidencing varying mood states, although the majority were euthymic. We re-ran the DTI analyses excluding the two youth with BP NOS; the results obtained were remarkably similar and remained statistically significant. Previous research suggests that psychotropic medications have limited impact on WM in BPD (Frazier et al. 2007), a finding supported by studies in schizophrenia which also failed to find a significant effect of medication on measures of diffusion (Lim et al. 1999; Foong et al. 2000). Finally, we did not have clinical data regarding family history of psychopathology or head trauma for the healthy comparison group that may affect WM.

Conclusions

These findings are important in that they provide additional evidence of WM disruption of CC genu in youth with BPD and, more specifically, in aggressive bipolar youth. Our exploratory investigations found evidence that the AC is disrupted in youth with BPD and preliminary evidence that the integrity of this tract is significantly associated with Life History of Aggression scores. This initial finding may be related to the purported role of the AC in the integration and processing of emotional information. However, additional studies with larger samples are needed to replicate these findings, as we could find no other studies reporting on bipolar youth with aggression, nor were we able to find other reports of a role for the AC in aggression regardless of psychiatric diagnosis.

Clinical Significance

Aggression is a construct that is a sensitive marker of the severity of BPD and can be reliably measured by utilizing empirically validated rating scales. Youth in whom BPD and Attention-Deficit/Hyperactivity Disorder have been diagnosed are found to exhibit significant levels of impulsive behavior and attention problems, but youth with BPD also exhibited significant levels of aggressive behavior, dysphoric mood (Doerfler et al. 2010), and functional impairments (Jensen et al. 2007). Thus, the pathophysiology of aggression in pediatric BPD warrants research focusing on biological markers that can address its etiology and eventually lead to targeted treatment interventions.

Disclosures

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References

- American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, 4th ed. (DSM-IV). Washington, DC: American Psychiatric Association; 1994.
- Axelson D, Birmaher B, Strober M, Gill MK, Valeri S, Chiappetta L, Ryan N, Leonard H, Hunt J, Iyengar S, Bridge J, Keller M: Phenomenology of children and adolescents with bipolar spectrum disorders. *Arch Gen Psychiatry* 63:1139–1148, 2006.
- Barnea-Goraly N, Chang KD, Karchemskiy A, Howe ME, Reiss AL: Limbic and corpus callosum aberrations in adolescents with bipolar disorder: A tract-based spatial statistics analysis. *Biol Psychiatry* 66:238–244, 2009.
- Basser PJ, Mattiello J, LeBihan D: MR diffusion tensor spectroscopy and imaging. *Biophys J* 66:259–267, 1994.
- Beaulieu C: The basis of anisotropic water diffusion in the nervous system—a technical review. *NMR Biomed* 15:435–455, 2002.
- Bellani M, Yeh PH, Tansella M, Balestrieri M, Soares JC, Brambilla P: DTI studies of corpus callosum in bipolar disorder. *Biochem Soc Trans* 37:1096–1098, 2009.
- Birmaher B, Axelson D: Course and outcome of bipolar spectrum disorder in children and adolescents: A review of the existing literature. *Dev Psychopathol* 18:1023–1035, 2006.
- Blumberg HP, Fredericks C, Wang F, Kalmar JH, Spencer L, Papademetris X, Pittman B, Martin A, Peterson BS, Fulbright RK, Krystal JH: Preliminary evidence for persistent abnormalities in amygdala volumes in adolescents and young adults with bipolar disorder. *Bipolar Disord* 7:570–576, 2005.
- Brambilla P, Bellani M, Yeh PH, Soares JC: Myelination in bipolar patients and the effects of mood stabilizers on brain anatomy. *Curr Pharm Des* 15:2632–2636, 2009.
- Carter TD, Mundo E, Parikh SV, Kennedy JL: Early age at onset as a risk factor for poor outcome of bipolar disorder. *J Psychiatr Res* 37:297–303, 2004.
- Chang K, Karchemskiy A, Barnea-Goraly N, Garrett A, Simeonova DI, Reiss A: Reduced amygdala gray matter volume in familial pediatric bipolar disorder. *J Am Acad Child Adolesc Psychiatry* 44:565–573, 2005.

- Chen BK, Sassi R, Axelson D, Hatch JP, Sanches M, Nicoletti M, Brambilla P, Keshavan MS, Ryan ND, Birmaher B, Soares JC: Cross-sectional study of abnormal amygdala development in adolescents and young adults with bipolar disorder. *Biol Psychiatry* 56:399–405, 2004.
- Clark DL, Boutros NN, Mendez MF: *The Brain and Behavior: An introduction to Behavioral Neuroanatomy*. New York: Cambridge University Press; 2010.
- Coccaro EF, Berman ME, Kavoussi RJ: Assessment of life history of aggression: Development and psychometric characteristics. *Psychiatry Res* 73:147–157, 1997.
- Conturo TE, Lori NF, Cull TS, Akbudak E, Snyder AZ, Shimony JS, McKinstry RC, Burton H, Raichle ME: Tracking neuronal fiber pathways in the living human brain. *Proc Natl Acad Sci U S A* 96:10422–10427, 1999.
- Cullen KR, Klimes-Dougan B, Muetzel R, Mueller BA, Camchong J, Hourri A, Kurma S, Lim KO: Altered white matter microstructure in adolescents with major depression: A preliminary study. *J Am Acad Child Adolesc Psychiatry* 49:173–183, 2010.
- DelBello MP, Zimmerman ME, Mills NP, Getz GE, Strakowski SM: Magnetic resonance imaging analysis of amygdala and other subcortical brain regions in adolescents with bipolar disorder. *Bipolar Disord* 6:43–52, 2004.
- Dickstein DP, Milham MP, Nugent AC, Drevets WC, Charney DS, Pine DS, Leibenluft E: Frontotemporal alterations in pediatric bipolar disorder: Results of a voxel-based morphometry study. *Arch Gen Psychiatry* 62:734–741, 2005.
- Doerfler LA, Connor DF, Toscano PF, Jr.: Aggression, ADHD symptoms, and dysphoria in children and adolescents diagnosed with bipolar disorder and ADHD. *J Affect Disord* 131:312–319, 2010.
- Dubois J, Dehaene-Lambertz G, Soares C, Cointepas Y, Le Bihan D, Hertz-Pannier L: Microstructural correlates of infant functional development: Example of the visual pathways. *J Neurosci* 28:1943–1948, 2008.
- Filley CM: White matter and behavioral neurology. *Ann N Y Acad Sci* 1064:162–183, 2005.
- Foong J, Maier M, Clark CA, Barker GJ, Miller DH, Ron MA: Neuropathological abnormalities of the corpus callosum in schizophrenia: A diffusion tensor imaging study. *J Neurol Neurosurg Psychiatry* 68:242–244, 2000.
- Frazier JA, Breeze JL, Papadimitriou G, Kennedy DN, Hodge SM, Moore CM, Howard JD, Rohan MP, Caviness VS, Makris N: White matter abnormalities in children with and at risk for bipolar disorder. *Bipolar Disord* 9:799–809, 2007.
- Grunebaum MF, Ramsay SR, Galfalvy HC, Ellis SP, Burke AK, Sher L, Printz DJ, Kahn DA, Mann JJ, Oquendo MA: Correlates of suicide attempt history in bipolar disorder: A stress-diathesis perspective. *Bipolar Disord* 8:551–557, 2006.
- Huang H, Fan X, Williamson DE, Rao U: White matter changes in healthy adolescents at familial risk for unipolar depression: A diffusion tensor imaging study. *Neuropsychopharmacology: Official publication of the American College of Neuropsychopharmacology* 36:684–691, 2011.
- Huang H, Zhang J, Jiang H, Wakana SP, L., Miller MI, van Zijl PCM, Hillis AE, Wytko R, Mori S: DTI tractography based parcellation of white matter: Application to the mid-sagittal morphology of corpus callosum. *NeuroImage* 26:195–205, 2005.
- Huppi PS, Murphy B, Maier SE, Zientara GP, Inder TE, Barnes PD, Kikinis R, Jolesz FA, Volpe JJ: Microstructural brain development after perinatal cerebral white matter injury assessed by diffusion tensor magnetic resonance imaging. *Pediatrics* 107:455–460, 2001.
- Jensen PS, Youngstrom EA, Steiner H, Findling RL, Meyer RE, Malone RP, Carlson GA, Coccaro EF, Aman MG, Blair J, Dougherty D, Ferris C, Flynn L, Green E, Hoagwood K, Hutchin-
 inson J, Laughren T, Leve LD, Novins DK, Vitiello B: Consensus report on impulsive aggression as a symptom across diagnostic categories in child psychiatry: Implications for medication studies. *J Am Acad Child Adolesc Psychiatry* 46:309–322, 2007.
- Jones DK, Horsfield MA, Simmons A: Optimal strategies for measuring diffusion in anisotropic systems by magnetic resonance imaging. *Magn Reson Med* 42:515–525, 1999.
- Kaufman J, Birmaher B, Brent D, Rao U, Flynn C, Moreci P, et al. Schedule for affective disorders and schizophrenia for school-age children-present and lifetime version (K-SADS-PL): Initial reliability and validity data. *J Am Acad Child Adolesc Psychiatry* 36:980–987, 1997.
- LeDoux JE: Emotion circuits in the brain. *Annu Rev Neurosci* 23:155–184, 2000.
- Leon AC, Shear MK, Klerman GL, et al. A comparison of symptom determinants of patient and clinician global ratings in patients with panic disorder and depression. *J Clin Psychopharmacol* 13:327–331, 1993.
- Lewinsohn PM, Klein DN, Seeley JR: Bipolar disorders in a community sample of older adolescents: Prevalence, phenomenology, comorbidity, and course. *J Am Acad Child Adolesc Psychiatry* 34:454–463, 1995.
- Lim KO, Hedehus M, Moseley M, de Crespigny A, Sullivan EV, Pfefferbaum A: Compromised white matter tract integrity in schizophrenia inferred from diffusion tensor imaging. *Arch Gen Psychiatry* 56:367–374, 1999.
- Neil JJ, Shiran SI, McKinstry RC, Scheffert GL, Snyder AZ, Almlil CR, Akbudak E, Aronovitz JA, Miller JP, Lee BC, Conturo TE: Normal brain in human newborns: Apparent diffusion coefficient and diffusion anisotropy measured by using diffusion tensor MR imaging. *Radiology* 209:57–66, 1998.
- Pavuluri MN, Yang S, Kamineni K, Passarotti AM, Srinivasan G, Harral EM, Sweeney JA, Zhou XJ: Diffusion tensor imaging study of white matter fiber tracts in pediatric bipolar disorder and attention-deficit/hyperactivity disorder. *Biol Psychiatry* 65:586–593, 2009.
- Perlis RH, Miyahara S, Marangell LB, Wisniewski SR, Ostacher M, DelBello MP, Bowden CL, Sachs GS, Nierenberg AA: Long-term implications of early onset in bipolar disorder: Data from the first 1000 participants in the systematic treatment enhancement program for bipolar disorder (STEP-BD). *Biol Psychiatry* 55:875–881, 2004.
- Rollins NK, Vachha B, Srinivasan P, Chia J, Pickering J, Hughes CW, Gimi B: Simple developmental dyslexia in children: Alterations in diffusion-tensor metrics of white matter tracts at 3 T. *Radiology* 251:882–891, 2009.
- Rush AJ, Trivedi MH, Ibrahim HM, Carmody TJ, Arnow B, Klein DN, Markowitz JC, Ninan PT, Kornstein S, Manber R, Thase ME, Kocsis JH, Keller MB: The 16-Item Quick Inventory of Depressive Symptomatology (QIDS), clinician rating (QIDS-C), and self-report (QIDS-SR): A psychometric evaluation in patients with chronic major depression. *Biol Psychiatry* 54:573–583, 2003.
- Smith SM, Jenkinson M, Johansen-Berg H, Rueckert D, Nichols TE, Mackay CE, Watkins KE, Ciccarelli O, Cader MZ, Matthews PM, Behrens TE: Tract-based spatial statistics: Voxelwise analysis of multi-subject diffusion data. *Neuroimage* 31:1487–1505, 2006.
- Tamnes CK, Ostby Y, Walhovd KB, Westlye LT, Due-Tønnessen P, Fjell AM: Intellectual abilities and white matter microstructure in development: A diffusion tensor imaging study. *Hum Brain Mapp* 31:1609–1625, 2010.
- Trivedi MH, Rush AJ, Ibrahim HM, Carmody TJ, Biggs MM, Suppes T, Crismon ML, Shores-Wilson K, Toprac MG, Dennehy EB, Witte B, Kashner TM: The Inventory of Depressive Symptomatology, Clinician Rating (IDS-C) and Self-Report (IDS-SR), and the Quick Inventory of Depressive Symptomatology, Clinician Rating

- (QIDS-C) and Self-Report (QIDS-SR) in public sector patients with mood disorders: A psychometric evaluation. *Psychol Med* 34:73–82, 2004.
- Versace A, Almeida JRC, Hassel S, Walsh ND, Novelli M, Klein CR, Kupfer DJ, Phillips ML: Elevated left and reduced right orbito-medial prefrontal fractional anisotropy in adults with bipolar disorder revealed by tract-based spatial statistics. *Arch Gen Psychiatry* 65:1041–1061, 2008.
- Womer FY, Kalmar JH, Wang F, Blumberg HP: A Ventral Prefrontal-Amygdala Neural System in Bipolar Disorder: A View from Neuroimaging Research. *Acta Neuropsychiatr* 21:228–238, 2009.
- Young RC, Biggs JT, Ziegler VE, Meyer DA: A rating scale for mania: Reliability, validity and sensitivity. *Br J Psychiatry* 133: 429–435, 1978.

Address correspondence to:

Kirti Saxena, M.D.

Department of Psychiatry

University of Texas Health Science Center at Houston

1941 East Road

Houston, TX 77054

E-mail: kirti.saxena@uth.tmc.edu