Original Investigation

White Matter Structure in Youth With Behavioral and Emotional Dysregulation Disorders
A Probabilistic Tractographic Study

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IMPORTANCE Psychiatric disorders in youth characterized by behavioral and emotional dysregulation are often comorbid and difficult to distinguish. An alternative approach to conceptualizing these disorders is to move toward a diagnostic system based on underlying pathophysiologic processes that may cut across conventionally defined diagnoses. Neuroimaging techniques have potentials for the identification of these processes.

OBJECTIVE To determine whether diffusion imaging, a neuroimaging technique examining white matter (WM) structure, can identify neural correlates of emotional dysregulation in a sample of youth with different psychiatric disorders characterized by behavioral and emotional dysregulation.

DESIGN, SETTING, AND PARTICIPANTS Using global probabilistic tractography, we examined relationships between WM structure in key tracts in emotional regulation circuitry (ie, cingulum, uncinate fasciculus, and forceps minor) and (1) broader diagnostic categories of behavioral and emotional dysregulation disorders (DDs) and (2) symptom dimensions cutting across conventional diagnoses in 120 youth with behavioral and/or emotional DDs, a referred sample of the Longitudinal Assessment of Manic Symptoms (LAM) study. Thirty age- and sex-matched typically developing youth (control participants) were included. Multivariate multiple regression models were used. The study was conducted from July 1, 2010, to February 28, 2014.

MAIN OUTCOMES AND MEASURES Fractional anisotropy as well as axial and radial diffusivity were estimated and imported into a well-established statistical package. We hypothesized that (1) youth with emotional DDs and those with both behavioral and emotional DDs would show significantly lower fractional anisotropy compared with youth with behavioral DDs in these WM tracts and (2) that there would be significant inverse relationships between dimensional measures of affective symptom severity and fractional anisotropy in these tracts across all participants.

RESULTS Multivariate multiple regression analyses revealed decreased fractional anisotropy and decreased axial diffusivity within the uncinate fasciculus in youth with emotional DDs vs those with behavioral DDs, those with both DDs, and the controls ($F_{6,160}$ = 2.4; P = .032; all pairwise comparisons, P < .002). In the same model, greater severity of manic symptoms was positively associated with higher fractional anisotropy across all affected youth ($F_{3,85}$ = 2.8; P = .044).

CONCLUSIONS AND RELEVANCE These findings suggest that abnormal uncinate fasciculus and cingulum WM structure may underlie emotional, but not behavioral, dysregulation in pediatric psychiatric disorders and that a different neural mechanism may exist for comorbid emotional and behavioral DDs.

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Most psychiatric disorders in youth include behavioral dysregulation disorders (DDs) that are often associated with emotional problems (eg, attention-deficit/hyperactivity disorder [ADHD]; disruptive behavior disorders [DBDs], including conduct disorder and oppositional defiant disorder); and emotional DDs that are often associated with behavioral problems (eg, depressive disorder, bipolar spectrum disorder [BPSD], and anxiety disorder). Given the overlap of symptoms and their high comorbidity, however, psychiatric disorders in youth pose challenges for diagnosis and treatment, increasing the use of "not otherwise specified" diagnoses.[1-4] Although diagnostic manuals represent the consensus standard for psychiatric diagnosis, research needs to establish a groundwork for a future diagnostic system based on underlying pathophysiologic processes by using frameworks that may cut across conventionally defined diagnoses.[5]

One possible approach is to conceptualize broad categories of disorders characterized by emotional dysregulation, behavioral dysregulation, or comorbid behavioral and emotional dysregulation. In this categorical approach, youth with emotional DDs may have comorbid behavioral problems, and youth with behavioral DDs may have associated emotional problems. Despite similar presentations of emotional and behavioral dysregulation across these broader categories of psychiatric disorders in youth, their underlying neural mechanisms may differ. Another approach conceptualizes these disorders in terms of dimensions of behavioral or emotional dysregulation that cut across conventionally defined diagnoses, paralleling the dimensional approach of the National Institute of Mental Health's Research Domain Criteria.[5]

Neuroimaging can help identify neural mechanisms underpinning behavioral and emotional dysregulation in youth. Diffusion imaging (DI) is a noninvasive technique sensitive to water diffusivity in brain tissue.[6,7] Diffusion imaging measures include axial diffusivity (L1), radial diffusivity (RD), and fractional anisotropy (FA), representing the degree of fiber coherence. Tracts with collinear axons (densely packed fibers) are mostly characterized by high FA and high L1, and tracts with noncollinear axons (eg, crossing fibers) are primarily characterized by low FA and high RD. White matter (WM) damage is most often characterized by low FA and high RD.

Changes in DI measures correlate with progressive cortical thinning[8] and synaptic pruning, a process by which redundant synapses overproduced early in life are eliminated.[9] Specifically, age-related increases in the magnitude and directionality of water diffusivity (ie, increased FA with increased L1 and/or decreased RD) may reflect ongoing maturation of axons and their myelin sheaths from childhood to adulthood.[10-15] In this time frame, ventrolimbic and dorsolimbic WM pathways may play a key role in the pathophysiology of many psychiatric disorders characterized by emotional dysregulation.[16-19] Specifically, the uncinate fasciculus, connecting the anterior temporal pole (including amygdala) with the prefrontal cortex and known to be involved in reappraisal strategy,[20] constitutes the ventrolimbic WM pathway.[21-24] The cingulum, connecting the anteromedial temporal lobe (including the amygdala-hippocampus) with the cingulate cortex, constitutes the dorsolimbic WM pathway.[22-24] Another tract supporting interhemispheric associative functions of emotion (and cognition) is the forceps minor of the corpus callosum, which connects the left and right prefrontal regions.[23,25,26] Examining whether WM abnormalities in these tracts are associated with emotional more than behavioral DDs in youth can provide neurobiological measures to help distinguish these disorders.

Diffusion imaging studies in psychiatric disorders in youth have focused on comparing youth with a conventionally defined diagnosis vs healthy youth. Studies in youth with BPSD reported WM abnormalities in the frontal[27,28] and temporal[27,29] regions as well as in the corpus callosum.[27,30-33] Similarly, in youth with depressive disorder, one study[34] reported lower FA in the uncinate and cingulum. White matter abnormalities in youth with ADHD have been reported in numerous tracts, including the forceps minor, uncinate,[35] and cingulum.[36,37] A recent study[38] also reported higher FA in the uncinate of youth with severe DBDs, disconfirming previous evidence.[39] Together, these findings suggest abnormalities in the uncinate, cingulum, and corpus callosum across a range of psychiatric disorders in youth characterized by emotional and behavioral dysregulation but a more consistent pattern of abnormal (decreased) FA in youth with emotional DDs (BPSD and depressive disorder) than in those with behavioral DDs (ADHD and DBDs). However, to our knowledge, no DI study adopted a broader categorical or dimensional approach to studying youth with behavioral and emotional DDs.

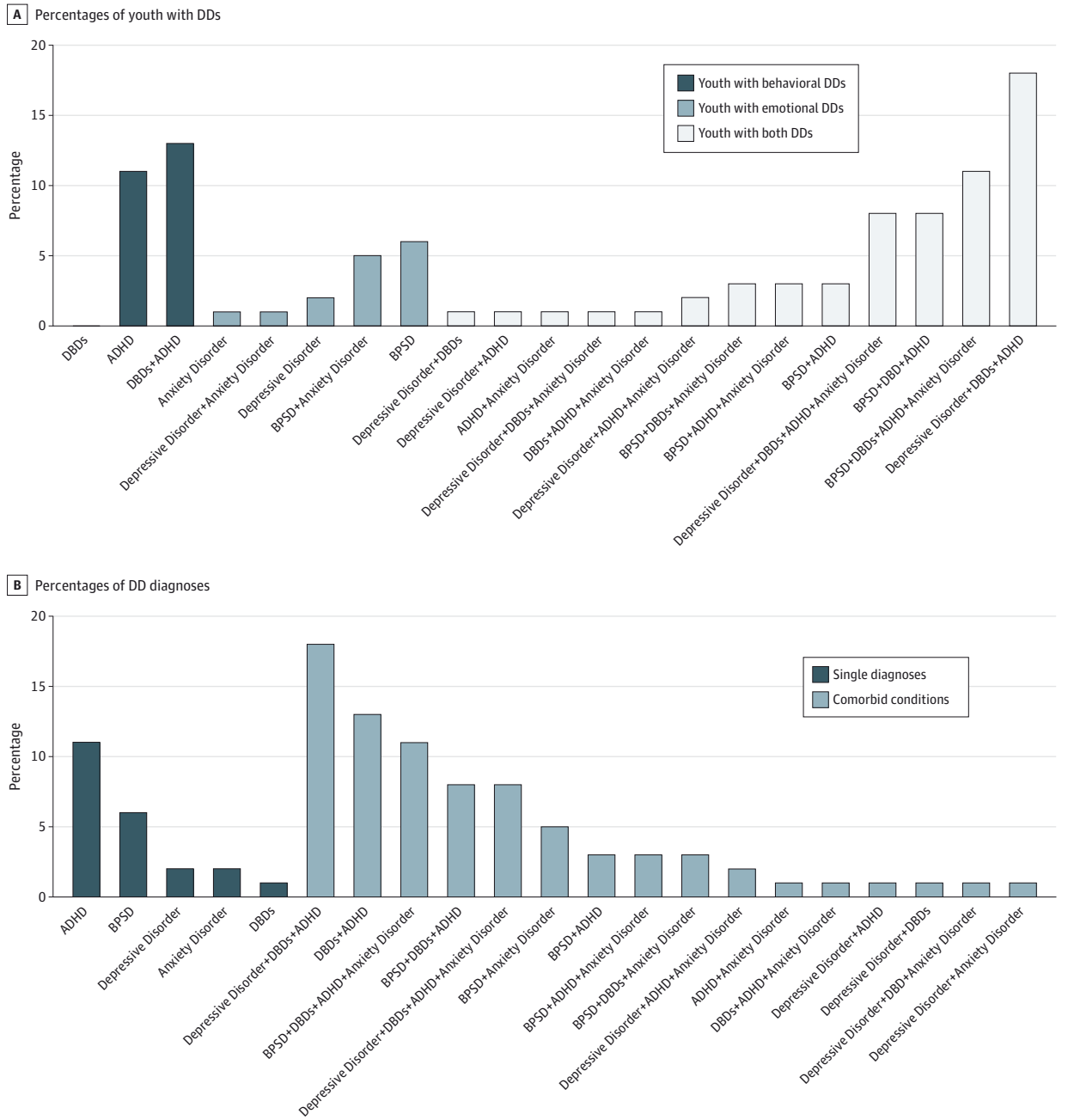
Recruiting from a multisite longitudinal study of youth seeking treatment for behavioral and emotional DDs (Longitudinal Assessment of Manic Symptoms [LAMS]),[40] we sought to identify relationships between emotional and behavioral DDs and WM in the above-described tracts in a clinically well-characterized cohort of referred youth. The study was conducted from July 1, 2010, to February 28, 2014.

Given the inconsistency of DI findings in the study of specific psychiatric disorders in youth, likely owing to relatively small sample sizes and region-of-interest/voxel-based approaches, we used Tracts Constrained by Underlying Anatomy (TRACULA, based on a global probabilistic tractographic algorithm).[41] Because it uses reproducible tracking protocols[42] validated on training subjects, TRACULA is suitable for the study of well-characterized WM tracts[43] in large samples.

We evaluated a broader categorical approach and a dimensional approach. In the first approach, we categorized youth into broader diagnostic categories of youth with behavioral DDs only (ADHD, DBDs, and ADHD plus DBDs), youth with emotional DDs only (BPSD, depressive disorder, anxiety disorder, BPSD plus anxiety disorder, and depressive disorder plus anxiety disorder), and youth with comorbid behavioral and emotional DDs (including combinations of the other 2 categories) (**Figure 1**A). The hypothesis for this approach was that youth with emotional DDs and those with both emotional and behavioral DDs would show significantly lower FA than would youth with behavioral DDs in the uncinate fasciculus, cingulum, and forceps minor.

The second approach was to determine the extent to which dimensional measures of emotional dysregulation, including measures of mania, depression, and anxiety as well as a mea-

Figure 1. Diagnostic Categories



A, Bar graph represents proportions and corresponding percentages of youth with behavioral dysregulation disorders (DDs), emotional DDs, *and* both DDs in the Longitudinal Assessment of Manic Symptoms (LAMS) study neuroimaging sample. B, Bar graph represents percentages of different diagnoses in LAMS study youth. Single diagnoses: attention deficit/hyperactivity disorder (ADHD) (11%), bipolar spectrum disorder (BPSD) (6%), disruptive behavior disorders (DBDs) (2%), depressive disorder (2%), and anxiety disorder (1%). Lifetime comorbidities (blue tones): depressive disorder + DBDs + ADHD (18%), DBDs + ADHD (13%), BPSD + DBDs + ADHD + anxiety disorder (11%), BPSD + DBDs + ADHD (8%), depressive disorder + DBDs + ADHD + anxiety disorder (8%), BPSD + anxiety disorder (5%), BPSD + ADHD (3%), BPSD + ADHD + anxiety disorder (3%), BPSD + DBDs + anxiety disorder (3%), depressive disorder + ADHD + anxiety disorder (2%), ADHD + anxiety disorder (1%), DBDs + ADHD + anxiety disorder (1%), depressive disorder + ADHD (1%), depressive disorder + anxiety disorder (1%), depressive disorder + DBDs (1%), and depressive disorder + DBDs + anxiety disorder (1%).

sure of emotional dysregulation (the Parent General Behavior Inventory-10 Item Mania Scale [PGBI-10M][44]), were significantly associated with FA in the above-described WM tracts across youth with behavioral and/or emotional DDs irrespective of diagnosis. Our hypothesis for this approach was that there would be significant inverse relationships between the dimensional measures described above and FA in these tracts across the LAMS study youth.

We recruited a group of demographically matched, typically developing youth (control participants) to examine the extent to which youth in each broader diagnostic group, or those with different levels of symptom severity, showed abnormal WM FA compared with the control group. We also examined L1, RD, and volume of the above-described WM tracts to interpret FA findings and explored the effect of the lifetime presence of each conventionally defined diagnosis on FA in these tracts.

Methods

Participants

A total of 120 LAMS study participants from 3 sites were involved in this study: Case Western Reserve University (n = 32); Cincinnati Children's Hospital Medical Center (n = 47), and University of Pittsburgh Medical Center (n = 45). Twenty-nine LAMS study youth were excluded owing to data loss (n = 4) or image artifacts (n = 25). The excluded individuals did not differ significantly in age, sex, or IQ from those included in the analyses ($P > .05$) (eMethods in the Supplement), leaving 91 LAMS study youth (male/female, 55/36; mean [SD] age, 13.8 [2.1] years; right-/left-handedness, 83/8; and mean [SD] IQ, 102.8 [17.3]) in the neuroimaging study.

Thirty-two individuals were recruited to serve as controls from Case Western Reserve University (n = 13), Cincinnati Children's Hospital Medical Center (n = 6), and University of Pittsburgh Medical Center (n = 13). After quality control procedures, 2 controls were excluded for image artifacts and 30 demographically matched individuals without a history of psychiatric illness were included. The eMethods in the Supplement reports on medications and exclusion criteria.

The study received institutional review board approval at all scan sites (Case Western Reserve University [09-10-28], Cincinnati Children's Hospital Medical Center [2010-3347], and University of Pittsburgh Medical Center [PRO10090442]). Parents or guardians provided written informed consent, and children provided written informed assent prior to study participation. Participants received monetary compensation and a framed picture of their structural neuroimaging scan.

Data Analysis

Symptom Assessment

To assess emotional dysregulation, the LAMS study youth and their parents/guardians completed the Kiddie Schedule for Affective Disorders and Schizophrenia (K-SADS) for School-Age Children Mania Rating Scale (K-MRS)[45] and Depression Rating Scale (K-DRS) to assess hypomania/mania and depressive symptoms, respectively, at the time of the scan (eTable 1 in the Supplement). The Screen for Child Anxiety Related Emotional Disorders (SCARED)[46] assessed anxiety symptoms every 6 months throughout the LAMS study and at the time of the scan. To assess behaviors associated with emotional dysregulation, parents or guardians completed the PGBI-10M[44,47] (eMethods in the Supplement) at every 6 months throughout the LAMS study; the present analyses used scores closest to the scan day (eTable 1 in the Supplement).

Diagnostic Categories

As confirmed by a licensed clinician using K-SADS–defined diagnoses (*DSM-IV* based), the 91 LAMS study youth had a variety of current (at the time of the scan) *DSM-IV* diagnoses (Figure 1B). In broader diagnostic categories, there were 22 youth with behavioral DDs, 16 with emotional DDs, and 53 with both DDs (eTable 1 in the Supplement).

Neuroimaging

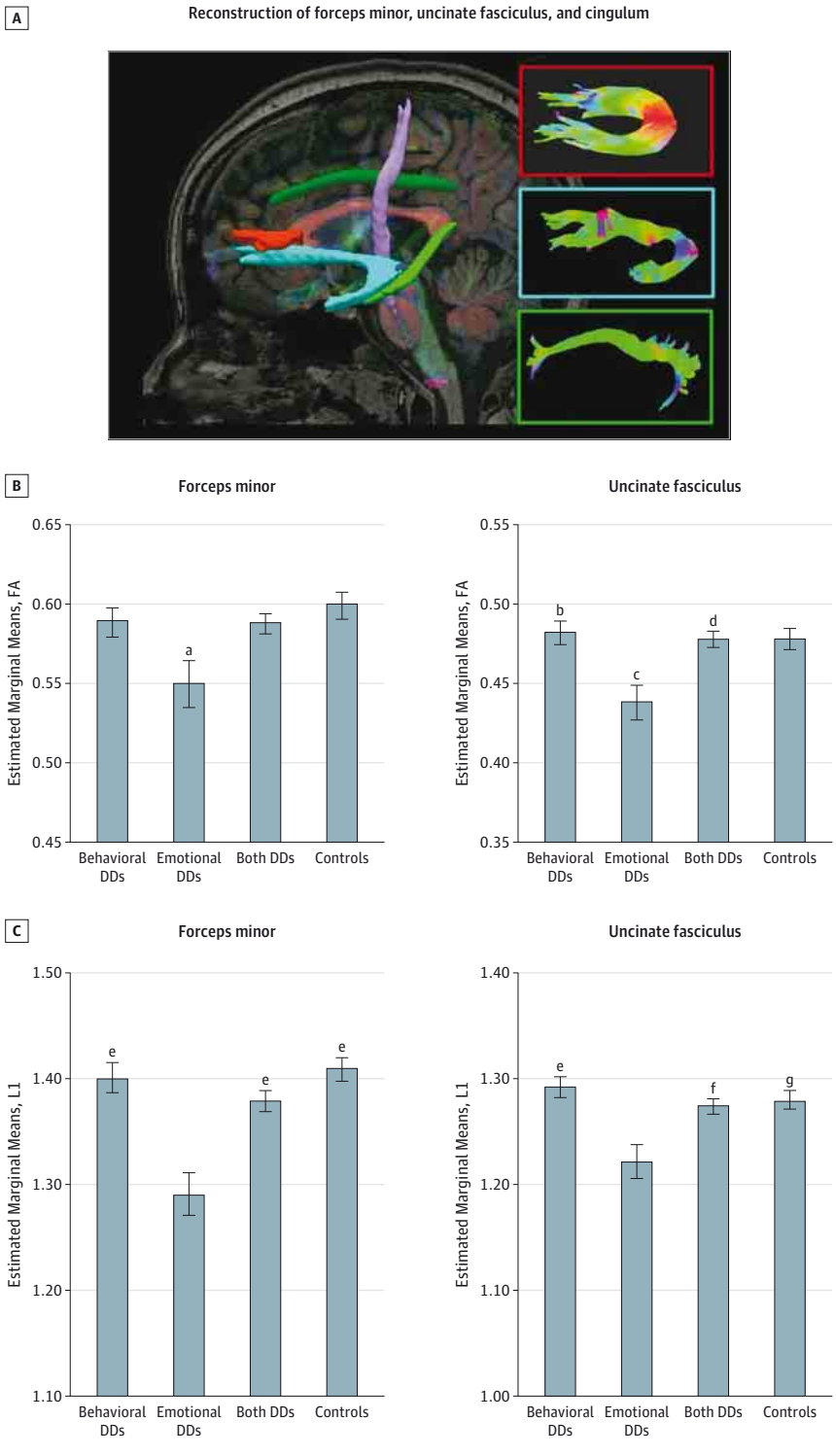
With the use of freely available software (ExploreDTI, version 4.8.4 [http://www.exploredti.com/] and FreeSurfer, version 5.3.0 [http://freesurfer.net/], including the TRACULA package), the 3 WM tracts described above were reconstructed in 121 participants (**Figure 2**A). The mean FA (plus L1, RD, and volume) was extracted for each pathway in each participant. The corticospinal tract was separately examined as a control region. Two trained independent observers (A.V. and H.A.) visually inspected all neuroimaging outputs to ensure data quality. Details on data acquisition and preprocessing are in the eMethods in the Supplement.

Statistical Analysis

Demographic, clinical, and DI measures were imported into well-established statistical software (SPSS, version 20; IBM Corporation) to test the main hypotheses and exploratory analyses. Rather than considering 3 WM tracts separately, we examined them simultaneously across the LAMS study youth, balancing type I and type II errors. To further reduce the number of multiple comparisons, we computed mean FA across both hemispheres for both bilateral tracts and then entered these values, together with values of the interhemispheric tract (forceps minor), into the same model (total, 3 WM tracts). The same approach was used for L1, RD, and volumetric measures.

To test the main hypotheses concurrently, we used a 4-level multivariate analytic approach. In the level 1 analyses, given numerous potential demographic and clinical variables to include in the model (ie, age, sex, handedness, IQ, parental educational level, and medication status [taking vs not taking psychotropic medications]), we examined the multivariate relationship between each independent variable (variables of interest or covariates) and the 3 dependent variables (FA across the 3 WM tracts) and, using a lenient threshold of $P < .10$, to allow inclusion of as many independent variables as possible in the final model and at the same time avoid model overfitting. In the level 2 analyses, only independent variables that demonstrated significant relationships with all 3 dependent variables were added to the final multivariate multiple regression model. In level 3 analyses, univariate analyses examined individual relationships between any independent variable (categorical or dimensional) and each dependent measure in significant findings from level 2 analyses. For the main effect of independent continuous variables on FA, estimated parameters were reported to assess the directionality of the relationship. In level 4 analyses, post hoc evaluations (independent *t* tests) were performed to interpret any significant finding arising from univariate analyses in the level 3 analyses. For

Figure 2. White Matter Tracts of Interest and Error Bar Graphs



A, Reconstruction of forceps minor (red), uncinate fasciculus (blue), and cingulum (green) in a study participant, using the global probabilistic algorithm proposed in TRACULA software. The corticospinal tract (purple) served as the control region. On the right side, 3 boxes indicate the same tracts reconstructed in the same participant using the deterministic algorithm proposed in ExploreDTI software for graphical comparison. Here, different colors within the tracts represent the orientation of the fiber segments (red, segments with a left-to-right orientation of the fibers; green, segments with an anterior-to-posterior orientation of the fibers; and blue, segments with an inferior-to-superior orientation of the fibers) based on the color coding convention used in diffusion imaging. B and C, Estimated marginal means and SEs of fractional anisotropy (FA) and axial diffusivity (L1), respectively, in forceps minor and uncinate fasciculus in youth with behavioral dysregulation disorder (DD), emotional DD, both DDs, and typically developing youth (controls) after controlling for study site and IQ.

[a] $P = .006$ vs controls.

[b] $P = .003$ vs youth with emotional DDs.

[c] $P = .005$ vs controls.

[d] $P = .002$ vs youth with emotional DDs.

[e] $P < .001$ vs youth with emotional DDs.

[f] $P = .004$ vs youth with emotional DDs.

[g] $P = .002$ vs youth with emotional DDs.

example, if level 3 analyses revealed a significant main effect of a broader diagnostic category on FA in 1 of the 3 WM tracts, then post hoc independent *t* tests determined the nature of between-group differences in this tract using Bonferroni corrections for the number of parallel between-group, post hoc comparisons. Correlational analyses examined any significant main effect of symptom dimension on any of the 3 dependent variables. The potential effect of laterality was examined using the same model proposed in the level 3 analyses. Here, left and right diffusivity measures for both bilateral tracts, rather than mean diffusivity measures, were entered into repeated-measures analyses.

Level 2 to 4 analyses were then repeated adding data from the control participants (matched for age, sex, IQ, parental educational level, and handedness). To further understand the nature of FA changes, mean L1, RD, and volume were examined, paralleling the level 2 to 4 analyses described above for FA.

Despite the high rate of comorbidities in this naturalistic sample, we decided to explore ($P < .05$) the effect of specific diagnoses within broader diagnostic categories on the main dependent variable (FA). The potential effect of each diagnosis (with vs without a specific disorder) in each of the 3 WM tracts was examined separately using univariate tests. Because anxiety disorder was predominantly a comorbid condition among 3 or 4 coexisting diagnoses (eMethods in the Supplement), we could not analyze the effect of having vs not having anxiety disorder.

To control for intersite differences in scanners, demographic variables, and proportion of diagnoses and treatments, the factor *site* was always entered in tested models (eTable 2 in the Supplement reports the effect of site). To control for intersite differences in signal to noise ratio, the ratio was estimated; the mean was determined across 68 images per participant and tested as a covariate in level 1 analyses (eTable 3 in the Supplement).

Results

Demographic and Clinical Characteristics

There were no significant between-group (LAMS study vs control youth) differences in age, sex ratio, handedness, parental educational level, and IQ. As expected, the LAMS study participants had significantly more anxious (SCARED), depressive (K-DRS), and manic (K-MRS) symptoms than did the controls (eTable 1 in the Supplement).

Diffusion Imaging

Level 1 Analyses

Multivariate analyses revealed no significant effect of demographic and other potential confounders, such as age, sex, parental educational level, handedness, or signal to noise ratio on FA. There was an effect of IQ on FA across the 3 WM tracts ($F_{3,85} = 2.5$; $P = .062$). After using a similar approach, no medication class (stimulant, nonstimulant, antidepressant, mood stabilizer, and antipsychotic) showed a main effect upon FA (eTable 2 and eTable 3 in the Supplement).

Multivariate analyses revealed a significant effect of broader diagnostic group ($F_{6,160} = 2.4$; $P = .032$) (eTable 3 in the Supplement) between youth with behavioral DDs, with emotional DDs, and with both DDs on FA across the 3 WM tracts, and a significant effect of K-MRS score on FA was noted across the 3 WM tracts ($F_{3,85} = 2.8$; $P = .044$) (eTable 3 in the Supplement). Thus, IQ, K-MRS score, and broader diagnostic group (and site) were entered as independent variables in level 2 analyses.

Level 2 Analyses

The main effects of broader diagnostic group and K-MRS score, but not IQ, remained significant in the final model ($F_{6,156} = 2.2$; $P = .047$ and $F_{3,78} = 2.3$; $P = .079$, respectively) (eTable 4 in the Supplement).

Level 3 Analyses

Univariate analyses revealed that the main effect of broader diagnostic group was in the forceps minor ($F_{2,80} = 3.3$; $P = .042$) and uncinate fasciculus ($F_{2,80} = 4.9$; $P = .009$), whereas the main effect of manic symptoms (K-MRS) was in the cingulum ($F_{1,80} = 4.2$; $P = .043$). Observation of parameter estimates revealed the cingulum to be a significant positive relationship (eTable 4 and eTable 5 in the Supplement).

Level 4 Analyses

Post hoc analyses revealed significantly lower FA in youth with emotional DDs vs those with both types of DDs ($P = .015$; Bonferroni corrected at .05/3 = .016 to control for 3 pairwise between-group comparisons) and a trend decrease in youth with emotional DDs vs those with behavioral DDs ($P = .025$) in the forceps minor. There was significantly lower FA in youth with emotional DDs than in those with behavioral DDs and with both DDs (all $P = .004$; Bonferroni corrected) in the uncinate fasciculus (eTable 4 in the Supplement and Figure 2B).

Level 2 to 4 Analyses With Controls

The main findings regarding significant independent variables in level 2 and 3 analyses described above remained after inclusion of the control group. There was significantly lower FA in youth with emotional DDs vs the controls in the forceps minor and uncinate fasciculus ($P = .006$ and $P = .005$, respectively; Bonferroni corrected at .05/3 = .017 to control for the 3 parallel comparisons) between each LAMS study broader diagnostic group and the control group (eTable 4 in the Supplement and Figure 2B). The positive relationship between the K-MRS score and FA in the cingulum remained significant across both the LAMS study and control groups ($P = .048$; level 3 analyses) but did not survive in post hoc analyses in LAMS study youth with K-MRS scores of 14 or above or below 14 vs the controls (footnote of eTable4 and eFigure 1 in the Supplement).

Level 2 to 4 Analyses of L1, RD, and Volume

These analyses revealed significantly lower L1 (but not RD or volume) in both the forceps minor and uncinate fasciculus in youth with emotional DDs vs those with behavioral DDs and with both DDs (and controls) (all $P < .004$), as well as a significant positive relationship between K-MRS and L1 in the cingulum ($P = .05$) using the same model applied for the analyses of FA (eTable 4 in the Supplement and Figure 2C).

As anticipated, the corticospinal tract was separately examined as a control region using one univariate analysis. We did not find any significant effect of group or symptom dimension in the control region (corticospinal tract) using dimensional or categorical measures (eTable 6 in the Supplement).

Exploratory Analyses: Effect of Conventional Diagnoses

Youth with ADHD (including those with "pure" ADHD or those with ADHD and any comorbid disorder) showed higher FA compared with youth without ADHD in the uncinate fasciculus ($P = .038$). Participants with DBDs (including

youth with "pure" DBDs or DBDs with any comorbid disorder) showed higher FA than did youth without DBDs in the uncinate fasciculus (P = .026) (eTable 7 and eFigure 2 in the Supplement). Youth without DBDs showed a lower trend for FA in the uncinate fasciculus compared with the control participants (P = .079).

Discussion

In 91 LAMS study youth with behavioral and emotional dysregulation, we sought to identify relationships between emotional dysregulation and WM structure in 3 major emotional regulation tracts. We examined the extent to which DI measures were associated with (1) broader diagnostic categories of behavioral and/or emotional DDs and (2) dimensions of emotional dysregulation severity. Supporting our broader categorical hypothesis, LAMS study youth with emotional DDs showed significantly lower FA (and L1) in the 3 WM tracts of interest than did youth with behavioral DDs and the control participants. Specifically, youth with emotional DDs demonstrated lower FA and lower L1 in the uncinate fasciculus (and, to a lesser extent, in the forceps minor) compared with youth with behavioral DDs, those with both DDs, and the control participants. The significantly lower L1 associated with lower FA may reflect a reduced number of axons and smaller axonal diameter in these tracts in youth with emotional DDs. These WM abnormalities may represent a neural mechanism of emotional dysregulation in youth. Indeed, decreased FA has been reported in these tracts in youth and adults with BPSD and depressive disorders[29,48-52] and evaluated in a meta-analysis.[53]

Participants with both DDs did not demonstrate lower FA in the above-described tracts compared with the controls, suggesting that emotional dysregulation symptoms in youth with behavioral DDs may have underlying neural mechanisms that are different from those of emotional DDs without behavioral dysregulation comorbidity. Unavailability of a more appropriate diagnostic category for youth presenting with both behavioral and emotional dysregulation may have contributed to a "default" diagnostic grouping of BPSD or depressive disorder comorbid with ADHD and/or DBDs. Additional evidence of a different pattern of WM abnormalities in youth with both DDs relative to youth with emotional DDs comes from our exploratory analyses based on conventionally defined diagnoses. Contrary to expectations, participants with BPSD or depressive disorder did not show lower FA in the uncinate fasciculus and/or forceps minor compared with those without these disorders. However, most youth with BPSD or depressive disorder also had comorbid ADHD/DBD, putting them in the *both* category, which may contribute to this null finding. Although youth with DBDs had significantly higher FA in the uncinate fasciculus than did youth without DBDs, as previously shown,[38] the group without DBDs (predominantly comprising youth with BPSD, depressive disorder, and/or anxiety disorder) demonstrated a lower trend of FA in the uncinate fasciculus vs the control participants, which is consistent with our main findings in youth with emotional DDs compared with the controls.

Although youth with emotional DDs experienced low levels of manic symptoms, possibly explained by fluctuating mood symptoms over time and medication effects,[54] there was a significant relationship between mania severity and cingulum FA and L1 across all LAMS study youth. Greater collinearity of cingulum axons may result in greater connectivity between the anterior cingulate cortex and temporal regions. Lower connectivity has been associated with functional impairment in pathologic vs healthy conditions[55,56]; however, the role of abnormally elevated WM connectivity in psychiatric disorders remains unclear.[30,37,38,57-65] Additional studies are needed to clarify the connectivity.

Further considerations from a developmental point of view are needed. Decreased uncinate fasciculus and forceps minor FA has been consistently associated with higher RD in adults with mood disorders,[51,52,62,66-68] suggestive of abnormal reorganization of axonal architecture (ie, high degree of noncollinear axons) and/or myelin or axonal damage. Lower L1 rather than higher RD, however, suggests an abnormally reduced number of collinear axons in these tracts in youth with emotional DDs. This reduction may lead to an abnormal compensatory increase of both collinear and noncollinear axons over development given findings of both higher RD and normal L1 in these tracts in adults with mood disorders.[51,52,62,66-68] Thus, the lower FA, associated with higher RD and normal L1, may underlie the patterns of aberrant functional connectivity between prefrontal regions and amygdala observed in adults with emotional DDs, such as BPSD.[69-71]

There are limitations to the present study. We used the mean FA (L1 and RD) across all voxels reconstructed within a tract of interest. We demonstrated significantly decreased FA in the uncinate fasciculus in youth with an emotional DD vs those with a behavioral DD and in those with both DDs. One interpretation of this finding is that there may be different neural mechanisms underpinning emotional dysregulation in youth with emotional DDs relative to youth with both DDs, but we cannot exclude the possibility that more subtle abnormalities in WM tracts, which may not have been captured by measurement of mean FA, may differentiate these 2 groups. Using a probabilistic algorithm based on a priori knowledge of well-known WM tracts (ie, global tractography), we focused on major WM tracts supporting emotional regulation.[21-24] We acknowledge that the involvement of other tracts, such as those in indirect cortico-thalamic-striatal-lenticular-cortical circuits, may also be important in emotional regulation. Additional studies using a more exploratory approach (eg, local tractography) are needed to examine other tracts, including those not primarily involved in emotional regulation. Diagnoses were mostly comorbid, reflecting the naturalistic design of this study. Additional studies should confirm our findings in noncomorbid psychiatric disorders in youth. Although there was no significant effect of psychotropic medications on WM, randomized clinical trial platforms would facilitate assessment of the effects of medications on WM tracts in psychiatric disorders in youth.

Conclusions

To our knowledge, this is the first study to implement broader diagnostic categories of behavioral and emotional DDs in neuroimaging. The proposed approach accounts for high rates of comorbidities in youth with psychiatric disorders and suggests that neural mechanisms underlying emotional dysregulation may differ between youth with emotional DDs and those with both emotional and behavioral DDs.

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