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White Matter Structure in Youth with Behavioral and Emotional Dysregulation Disorders: a Probabilistic Tractographic Study

Amelia Versace, M.D.[1], **Heather Acuff, B.S.**[2], **Michele A. Bertocci, Ph.D.**[1], **Genna Bebko, Ph.D.**[1], **Jorge R. C. Almeida, M.D., Ph.D.**[1], **Susan B. Perlman, Ph.D.**[1], **Alexander Leemans, Ph.D.**[3], **Claudiu Schirda, Ph.D.**[1], **Haris Aslam, B.A.**[1], **Amanda Dwojak, B.A.**[1], **Lisa Bonar, B.S.**[1], **Michael Travis, M.D.**[1], **Mary Kay Gill, R.N., M.S.N.**[1], **Christine Demeter, M.A.**[4], **Vaibhav A. Diwadkar, Ph.D.**[5], **Jeffrey L. Sunshine, M.D., Ph.D.**[4], **Scott K Holland, Ph.D.**[6], **Robert. A. Kowatch, M.D., Ph.D.**[7], **Boris Birmaher, M.D.**[1], **David Axelson, M.D.**[10], **Sarah M. Horwitz, Ph.D.**[8], **Thomas W. Frazier, Ph.D.**[9], **L. Eugene Arnold, M. D., M.Ed.**[10], **Mary. A Fristad, Ph.D, ABPP.**[10], **Eric A. Youngstrom, Ph.D.**[11], **Robert L. Findling, M.D, M.B.A.**[4,12], and **Mary L. Phillips, M.D., M.D.(Cantab)**[1]

[1]Department of Psychiatry, Western Psychiatric Institute and Clinic, University of Pittsburgh Medical Center, University of Pittsburgh. [2]Medical Science Training Program, University of Pittsburgh School of Medicine. [3]Image Sciences Institute, University Medical Center Utrecht, Utrecht, The Netherlands. [4]University Hospitals Case Medical Center/Case Western Reserve University. [5]Department of Psychiatry and Behavioral Neuroscience, Wayne State University. [6]Cincinnati Children's Hospital Medical Center, University of Cincinnati. [7]The Research Institute at Nationwide Children's Hospital. [8]Department of Child and Adolescent Psychiatry, New York University School of Medicine. [9]Pediatric Institute, Cleveland Clinic. [10]Department of Psychiatry, Ohio State University. [11]Department of Psychology, University of North Carolina at Chapel Hill. [12]Department of Psychiatry, Johns Hopkins University.

Abstract

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 can identify neural correlates of emotional dysregulation in a sample of youth with a variety of different psychiatric disorders characterized by behavioral and emotional dysregulation.

Corresponding Author: Amelia Versace, Western Psychiatric Institute and Clinic, Loeffler Building, room 215, 121 Meyran Avenue, Pittsburgh, PA 15213, 412-383-8131, versacea@upmc.edu.

Conflict of Interest: Drs. Versace, Acuff, Bertocci, Bebko, Almeida, Perlman, Leemans, Schirda, Aslam Dwojak, Bonar, Travis, Gill, Demeter, Diwadkar, Sunshine, Holland, Kowatch, Birmaher, Axelson, Horwitz, Fristad, Youngstrom, and Phillips have no competing financial interest to report.

Design, Setting, and Participants—Start date = 07/01/10; End date = 02/28/15. We examined relationships between WM structure in key tracts in emotional regulation circuitry 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. Thirty typically developing youth (control participants) were included.

Main Outcome Measure(s)—Using global probabilistic tractography, key WM tracts in emotional regulation circuitry (ie, cingulum, uncinate fasciculus, and forceps minor) were reconstructed. Fractional anisotropy (and axial or radial diffusivity) was estimated, and values were 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 statistically significantly decreased fractional anisotropy and decreased axial, but not increased radial, diffusivity, within the uncinate fasciculus, in youth with emotional DDs vs. those *with*-behavioral DDs, vs those with both DDs, and vs controls (F P all pairwise comparisons, $p<0.002$). In the same model, greater severity of manic symptoms was *positively* associated with higher fractional anisotropy across all affected youth (F P $p=0.043$).

Conclusions and Relevance—The findings of the present study 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.

Keywords

Behavioral Dysregulation; Emotional Dysregulation; Diffusion Imaging; Cingulum; Forceps Minor; Uncinate Fasciculus

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The majority of psychiatric disorders in youth (PDY) include behavioral dysregulation disorders, that are often associated with emotional problems, (eg,attention deficit hyperactivity disorder [ADHD], disruptive behavior disorders [DBD], including conduct disorder and oppositional defiant disorder) and emotional dysregulation disorders, often associated with behavioral problems, e.g.,depressive disorder(DD); bipolar spectrum disorders(BPSD); anxiety disorders(AXD). Given the overlap of symptoms and their high comorbidity, however, PDY pose challenges for diagnosis and treatment, increasing the use of 'Not Otherwise Specified' diagnoses[1-4]. While 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, using frameworks that may cut across conventionally-defined diagnoses[5].

One possible approach is to conceptualize broad categories of disorders characterized by either emotional dysregulation, behavioral dysregulation, or comorbid behavioral and emotional dysregulation. In this categorical approach, youth with emotional dysregulation disorders may have comorbid behavioral problems, while youth with behavioral

dysregulation disorders may have associated emotional problems. Despite similar presentations of emotional and behavioral dysregulation across these broader categories of PDY, 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 NIMH's Research Domain Criteria[5].

Neuroimaging can help identify neural mechanisms underlying the pathophysiology of behavioral and emotional dysregulation in youth. Diffusion imaging (DI) is a non-invasive technique, sensitive to water diffusivity in brain tissue[6,7]. DI 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 non-collinear axons(e.g.,crossing fibers) by low FA and high RD; while WM damage is mostly 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/directionality of water diffusivity(i.e., 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 timeframe, ventro- and dorso-limbic 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 prefrontal cortex and known to be involved in reappraisal strategy,[20] constitutes the *ventro-limbic WM pathway*[21-24]. The cingulum, connecting the anteromedial temporal lobe –including amygdala-hippocampus- with cingulate cortex, constitutes the *dorso-limbic WM pathway*[22-24]. Another tract supporting interhemispheric associative functions of emotion(and cognition) is the forceps minor of the corpus callosum, connecting left-right prefrontal regions[23,25,26]. Examining whether WM abnormalities in these tracts are associated with emotional more than behavioral dysregulation disorders in youth can provide neurobiological measures to help distinguish these disorders.

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

Recruiting from a multisite longitudinal study of youth seeking treatment for behavioral and emotional dysregulation, the Longitudinal Assessment of Manic Symptoms(LAMS) study[40], we sought to identify relationships between emotional, and behavioral, dysregulation disorders and WM in the above tracts in a clinically well-characterized cohort of referred youth.

Given the inconsistency of DI findings in the study of specific PDY, likely due to relatively small sample sizes and Region-Of-Interest/Voxel-Based approaches, we employed global probabilistic tractography, 'TRActs-Constrained-by-UnderLying-Anatomy'(TRACULA)[41]. Using 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 the following aims and hypotheses:

Broader Categorical Approach

We categorized youth into broader-diagnostic categories of youth with behavioral dysregulation disorders only(*with-BehavioralDD*; including ADHD,DBD,ADHD+DBD), youth with emotional dysregulation disorders only(*with-EmotionalDD*; including BPDS,DD,AXD,BPDS+ADX,DD+AXD), and youth with comorbid behavioral and emotional dysregulation disorders(*with-Both*; including combinations of the other 2classes.Figure-1A). **Hypothesis.1:** Youth *with-EmotionalDD*(and youth *with-Both*) would show significantly lower FA than youth *with-BehavioralDD* in uncinate fasciculus, cingulum, and forceps minor.

Dimensional Approach

To determine the extent to which dimensional measures of emotional dysregulation, including measures of mania, depression, anxiety, and a measure of emotional dysregulation, the Parent General Behavior Inventory-10 Item Mania Scale(PGBI-10M score) were significantly associated with FA in the above WM tracts across youth with behavioral and/or emotional dysregulation disorders, irrespective of diagnosis. **Hypothesis. 2:** There would be significant inverse relationships between the above dimensional measures and FA in these tracts across LAMS youth.

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

Methods

Participants

One-hundred-twenty LAMS participants from three sites participated: Case Western Reserve University(CWRU;n=32); Cincinnati Children's Hospital(CCH;n=47); and University of Pittsburgh Medical Center(UPMC;n=45). Thirty LAMS youth were excluded

due to data loss(n=4) or image artifacts(n=26). Those excluded did not differ significantly from those included in age, sex, or IQ(p>0.05;eMaterials), leaving 91 LAMS youth (male/female=55/36;mean-age[SD]=13.8[2.1];right/left handedness=83/8; IQ[SD]=102.8[17.3]) in the neuroimaging study.

32CONT were recruited from CWRU(n=13), CCH(n=6) and UPMC(n=13). After quality-control procedures(2CONT were excluded for image artifacts), 30demographically-matched CONT without history of psychiatric illness were included. eMaterials report medications and exclusion criteria.

Data analysis

Symptom Assessment—To assess emotional dysregulation, LAMS youth and their parents/guardians completed the Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children Mania Rating Scale(K-MRS) and Depression Rating Scale(K-DRS)[44] to assess hypo/mania and depressive symptoms, respectively, at scan(eTable-1). The Screen for Child Anxiety and Related Emotional Disorders(SCARED)[45] assessed anxiety symptoms at 6-monthly intervals throughout LAMS and at scan. To assess behaviors associated with emotional dysregulation, parents/guardians completed the PGBI-10M[46,47](eMaterials) at 6-monthly intervals throughout LAMS; present analyses usedscores closest to scan day.(eTable-1).

Diagnostic Categories—As confirmed by a licensed clinician using K-SADS defined-diagnoses(DSM-IV-based), the 91 LAMS youth had a variety of current(at scan) DSM-IV diagnoses.(Figure-1B). In broader-diagnostic categories, there were 22 youth *with-BehavioralDD*, 16 *with-EmotionalDD*, and 53 *with-Both*.(eTable-1).

Neuroimaging—Using freely-available softwares(ExploreDTI;FreeSurfer;TRACULA), the 3WM tracts described above were reconstructed in 121 participants(Figure-2A). 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(AV;HA) visually inspected all neuroimaging outputs to ensure data quality. Details on data acquisition and preprocessing are in eMaterials.

Statistical Approach

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

To test main hypotheses concurrently, we adopted the following multivariate analytic approach. *Level-1 Analyses:* Given numerous potential demographic and clinical variables to include in the model(i.e.,age, sex, handedness, IQ, parental education, medication status:

taking versus not-taking psychotropic medications), we examined the multivariate relationship between each individual independent variable(variables of interest and covariates) and 3 dependent variables(FA across the 3WM tracts) and, using a lenient threshold of $p<0.1$ to allow inclusion of as many independent variables as possible in the final model, but at the same time avoid model overfitting. *Level-2 Analyses:* Only those independent variables that demonstrated significant relationships with all 3 dependent variables were then added to the final multivariate multiple regression model. *Level-3 Analyses:* Univariate analyses examined individual relationships between any(categorical or dimensional) independent variable and each dependent measure in significant findings from Level-2 Analyses. For the main effect of independent continuous variables upon FA, estimated parameters were reported to assess the directionality of the relationship. *Level-4 Analyses:* *Post-hoc* analyses(independent t-tests) were performed to interpret any significant finding arising from univariate analyses in Level-3 Analyses above. For example, if Level-3 Analyses revealed a significant main effect of broader-diagnostic category upon FA in one of the 3WM 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 upon any of the 3 dependent variables. Using the same model proposed in Level-3, the potential effect of laterality was also examined. Here, left and right diffusivity measures for both bilateral tracts, rather than mean diffusivity measures, were entered into repeated measures analyses.

Level 2-4 Analyses were then repeated adding CONT(matched for age, sex, IQ, parental education, handedness).

To further understand the nature of FA changes, mean L1, RD, and volume were also examined, paralleling Level 2-4 Analyses performed above for FA.

Despite high rate of comorbidities in this naturalistic sample, we wished to explore($p<0.05$) the impact of specific diagnoses within broader-diagnostic categories on main dependent variables(FA). The potential effect of each individual diagnosis(with vs.without) in each of the three WM tracts was separately examined, using univariate tests. Because AXD was predominantly a comorbid condition among 3-4 coexisting diagnoses(eMaterials), we could not analyze the impact of having AXD vs. not.

Inter-site variability—To control for inter-site differences in scanners, demographic variables, and proportion of diagnoses/treatments, the factor ‘site’ was always entered in tested models(eTable-2 reports the effect of site). To control for inter-site differences in signal to noise ratio(SNR), SNR was estimated and averaged across 68 images per participant, and tested as a covariate in Level-1 Analyses.

Results

Demographic and Clinical Characteristics

There were no significant between-group(LAMS youth vs. CONT) differences in age, gender ratio, handedness, parental education and IQ. As expected, LAMS youth had

significantly more anxious(SCARED), depressive(K-DRS) and manic(K-MRS) symptoms than CONT(eTable-1).

DI

Level-1 Analyses—Multivariate analyses revealed no significant effect of demographic and other potential confounders, such as age, gender, parental education, handedness or SNR upon FA. There was an effect of IQ upon FA across the 3WM tracts($F_{[3,85]}$=2.5;p=0.062). Using a similar approach, no medication class(stimulants, non-stimulants, antidepressants, mood stabilizers, antipsychotics) showed a main effect upon FA. (Table-1; eTable-2).

Multivariate analyses revealed a significant effect of broader-diagnostic group($F_{[6,160]}$=2.4;p=0.032;Table-1) between youth *with-BehavioralDD, with-EmotionalDD* and *with-Both* upon FA across the 3WM tracts, and a significant effect of K-MRS upon FA across the 3WM tracts($F_{[3,85]}$=2.8;p=0.044;Table-1).

Thus, IQ, K-MRS and broader-diagnostic group(and site) were entered as independent variables in Level-2 Analyses.

Level-2 Analyses—Main effects of broader-diagnostic group and K-MRS, *but not IQ*, remained significant in the final model($F_{[6,156]}$=2.2;p=0.047 and $F_{[3,78]}$=2.3;p=0.079). (Table-2).

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=0.042) and uncinate fasciculus($F_{[2,80]}$=4.9;p=0.009) whereas the main effect of manic symptoms(K-MRS) was in the cingulum($F_{[1,80]}$=4.2;p=0.043). Observation of parameter estimates revealed the latter to be a significant positive relationship(Table-2;eTable-3).

Level-4 Analyses—*Post-hoc* analyses revealed significantly lower FA in youth *with-EmotionalDD* vs. those *with-Both*(p=0.015; Bonferroni corrected at 0.05/3=0.016, to control for three pairwise between-group comparisons), and a trend-decrease in youth *with-EmotionalDD* vs. those *with-BehavioralDD(*p=0.025) in forceps minor. There was significantly lower FA in youth *with-EmotionalDD* vs. those *with-BehavioralDD* and *with-*Both(both p=0.004; Bonferroni corrected) in uncinate fasciculus(Table-2;Figure-2B).

Level 2-4 Analyses with CONT—Main findings regarding significant independent variables in Level 2-3 Analyses above remained after inclusion of CONT. There was significantly lower FA in youth *with-EmotionalDD* vs. CONT in forceps minor and uncinate fasciculus(p=0.006 and p=0.005; Bonferroni corrected at 0.05/3=0.017 to control for the three parallel comparisons between each LAMS broader-diagnostic group and CONT; eTable-4A;Figure-2B). The positive relationship between K-MRS and FA in the cingulum remained significant across LAMS youth and CONT(p=0.048;*Level-3 Analyses*), but did not survive in *post-hoc* analyses in LAMS youth *with*-K-MRS≥14 or *with*-K-MRS<14 vs. CONT(Footnote of eTable-4A;eFigure-1).

Level 2-4 Analyses of L1, RD and volume—These analyses revealed significantly lower L1(but not RD or volume) in both forceps minor and uncinate in youth *with-EmotionalDD* vs. those *with-BehavioralDD* and *with-Both(*and CONT)(all p<0.004), and a significant positive relationship between K-MRS and L1 in the cingulum(p=0.05), using the same model used for the analyses of FA.(eTable-4B-D;Figure-2C).

We did not find any significant effect of group or symptom dimension in the control region(corticospinal tract) using dimensional or categorical measures.(eTable-5).

Exploratory analyses: effect of conventional diagnoses—Youth *with-ADHD*(including youth with 'pure'ADHD, or ADHD comorbid with any other disorder) showed higher FA vs.youth *without*-ADHD in the uncinate(p=0.038). Youth *with-DBD*(including youth with 'pure'DBD, or DBD comorbid with any other disorder) showed higher FA vs. youth *without-DBD* in the uncinate(p=0.026; eTable-6 for further details regarding the effect of conventional diagnoses; eFigure-2). Youth *without-DBD* showed trend-lower FA in the uncinate vs.CONT(p=0.079).

Discussion

In 91 LAMS youth with behavioral and emotional dysregulation, we sought to identify relationships between behavioral and 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 dysregulation disorders, and 2) dimensions of emotional dysregulation severity. Supporting our broader categorical hypothesis, LAMS youth *with-EmotionalDD* showed significantly lower FA(and L1) in the 3WM tracts of interest than youth *with-BehavioralDD* and CONT. Specifically, youth *with-EmotionalDD* showed lower FA and lower L1 in the uncinate fasciculus(and to a lesser extent in the forceps minor) vs. youth *with-BehavioralDD*, youth *with-Both* and CONT. The significantly lower L1, associated with lower FA, may reflect a reduced number of axons/smaller axonal diameter in these tracts in youth *with-EmotionalDD*. These WM abnormalities may represent a neural mechanism of emotional dysregulation in youth. Indeed, decreased FA has previously been reported in these tracts in youth and adults with BPSD and DD[29,48-52](for a meta-analysis, see[53]).

Interestingly, youth *with-Both*(vs.CONT) did not show lower FA in the above tracts, suggesting that emotional dysregulation symptoms in youth with behavioral dysregulation disorders may have different underlying neural mechanisms from emotional dysregulation disorders 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 DD comorbid with ADHD/DBD. Additional evidence for a different pattern of WM abnormalities in youth *with-Both* relative to youth *with-EmotionalDD* comes from our exploratory analyses based on conventionally-defined diagnoses. Contrary to expectations, youth *with-BPSD*(or *with-DD*) did not show lower FA in the uncinate and/or forceps minor versus those *without*-(these)*disorders*. However, most youth with BPSD or DD also had comorbid ADHD/DBD, putting them in the "Both" category, which may contribute to this

null finding. While youth *with-DBD* had significantly higher FA in the uncinate than youth *without-DBD*, as previously shown[38], the *without*-DBD group(predominantly comprising youth *with-BPSD*, *DD* and/or *ANX*) showed trend-lower FA in the uncinate vs. CONT, consistent with our main findings in youth *with-EmotionalDD* vs. CONT.

Although youth *with-EmotionalDD* showed 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 youth. Greater collinearity of cingulum axons may result in greater connectivity between anterior cingulate cortex and temporal regions. While lower connectivity has been associated with functional impairment in pathologic vs. healthy conditions[55,56]; the role of abnormally elevated WM connectivity in psychiatric disorders remains unclear[30,37,38,57-65]. Further studies are needed to clarify this.

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(i.e.,high degree of non-collinear 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-EmotionalDD*. This may lead to an abnormal, compensatory increase of both collinear and non-collinear 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]. This may underlie the patterns of aberrant functional connectivity between prefrontal regions and amygdala observed in adults with emotional dysregulation disorders such as BPSD[69-71].

There are limitations to the present study. We used the averaged FA(L1 and RD) across all voxels reconstructed within a tract of interest. We show significantly decreased FA in the uncinate fasciculus in youth *with-EmotionalDD* vs. those *with-BehavioralDD*, and those *with-Both*. One interpretation is that there may be different neural mechanisms underpinning emotional dysregulation in youth *with-EmotionalDD* relative to youth *with-Both*, 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 two groups. Using a probabilistic algorithm based on a-priori knowledge of well-known WM tracts(i.e., 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. Further studies employing a more exploratory approach(e.g., local tractography) are needed to examine additional tracts, including those not primarily involved in emotional regulation. Diagnoses were mostly comorbid, reflecting the naturalistic nature of this study. Further studies should confirm our findings in noncomorbid PDY. While there was no significant effect of psychotropic medications upon WM, randomized clinical trial platforms would facilitate assessment of effects of medications upon WM tracts in PDY.

Conclusions

This is the first study to implement broader-diagnostic categories of behavioral and emotional dysregulation in neuroimaging. The proposed approach accounts for high rates of PDY comorbidities, and suggests that neural mechanisms underlying emotional dysregulation may differ between youth *with-EmotionalDD* and youth *with-Both*.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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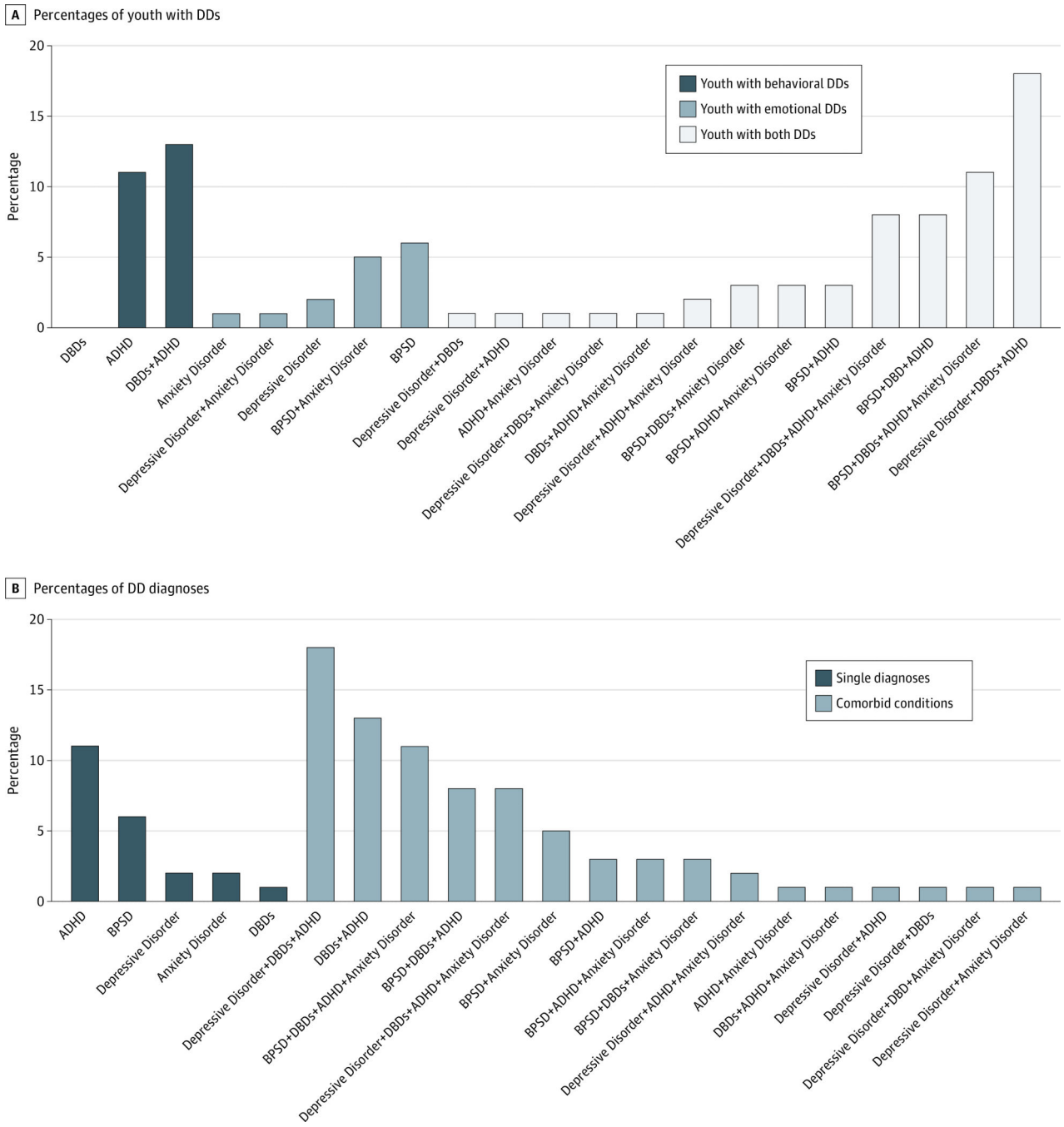

Figure-1.

Panel A. Pie graph represents proportions and corresponding percentages of youth *with-BehavioralDD*(in blue), youth *with-EmotionalDD*(in red) and youth *with-Both*(in purple) in the LAMS neuroimaging sample.

Panel B. Pie graph represents proportions and corresponding percentages of different diagnoses in LAMS youth. Single diagnoses(blue tones): ADHD(11%), BPSD(6%), DBD(2%), DD(2%), and AXD(1%). Lifetime comorbidities(grey tones): DD+DBD +ADHD(18%), DBD+ADHD(13%), BD+DBD+ADHD+AXD(11%), BD+DBD

+ADHD(8%), DD+DBD+ADHD+AXD(8%), BD+AXD(5%), BD+ADHD(3%), BD +ADHD+AXD(3%), BD+DBD+AXD(3%), DD+ADHD+AXD(2%), ADHD+AXD(1%), DBD+ADHD+AXD(1%), DD+ADHD(1%), DD+AXD(1%), DD+DBD(1%), DD+DBD +AXD(1%).

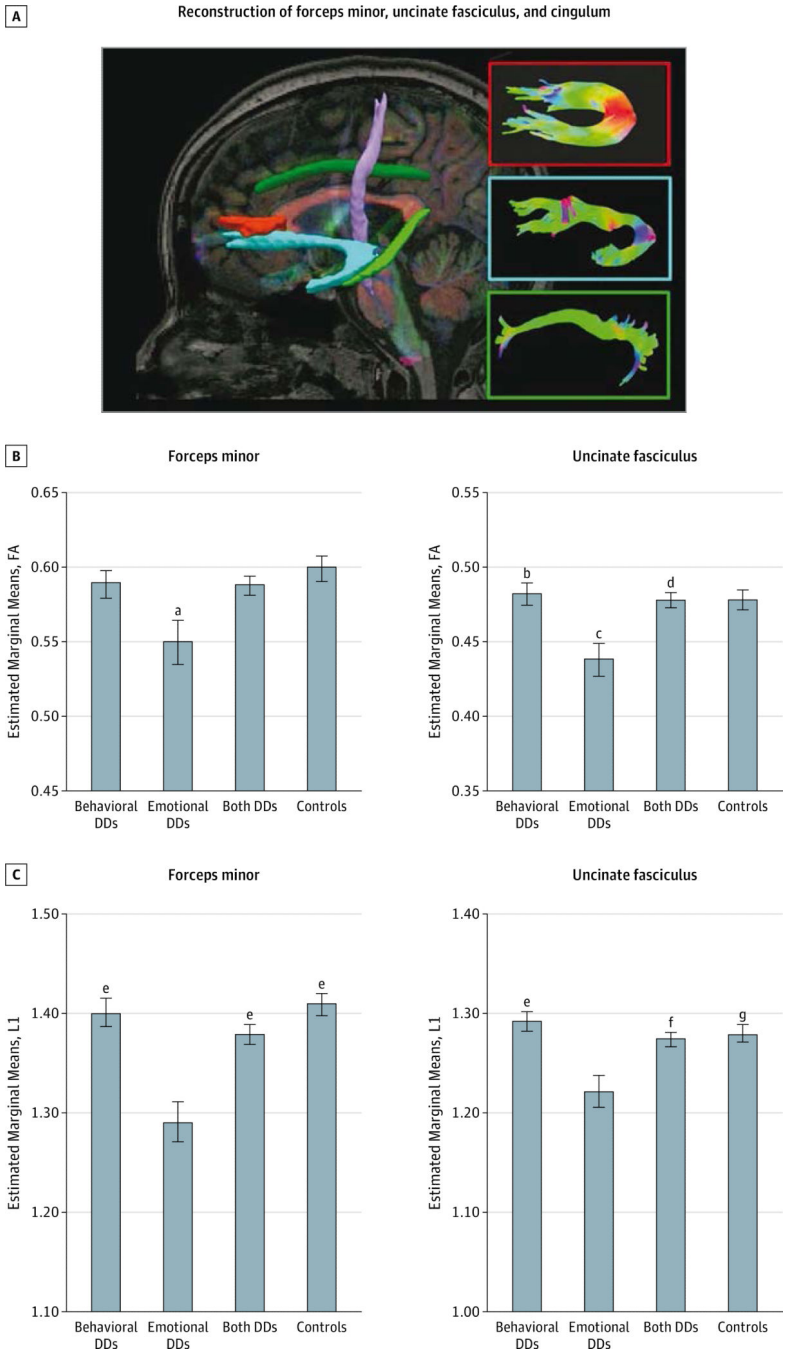

Figure-2.

Panel A. Reconstruction of *forceps minor(*red), *uncinate fasciculus(*blue) and *cingulum*(green) in one of our participants, using the global probabilistic algorithm proposed in TRACULA. The *cortico-spinal tract(*purple) served as 'control region'. On the left side, three boxes show the same tracts reconstructed in the same participant using the deterministic algorithm proposed in ExploreDTI, for graphical comparison. Here, different colors within 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; *blue*: segments with an inferior to superior orientation of the fibers), based on the color coding convention used in DI.

Panel B. Estimated Marginal Means and Standard Error of FA in forceps minor(left) and uncinate fasciculus(right) in youth *with-BehavioralDD*(in blue), youth *with-EmotionalDD*(in red), youth *with-Both*(in purple) and CONT(in green), after controlling for site and IQ.

Panel C. Estimated Marginal Means and Standard Error of L1 in forceps minor(left) and uncinate fasciculus(right) in youth *with-BehavioralDD*(in blue), youth *with-EmotionalDD*(in red), youth *with-Both*(in purple) and CONT(in green), after controlling for site and IQ.

FA: fractional anisotropy; IQ: intelligence quotient; Youth with-Behav.DD: youth with behavioral dysregulation disorders; Youth with-Emot.DD: youth with emotional dysregulation disorders; Youth with-Both: youth with both behavioral and emotional dysregulation disorders, CONT: typically developing youth.

Table-1 *Level-1 Analyses.* Multivariate Analyses upon FA(forceps minor, cingulum and uncinate fasciculi)

Effect of DEMOGRAPHIC and CLINICAL VARIABLES			
POTENTIAL CONFOUNDERS	**Wilks' Lambda**	**STATS**	**Sig.**
AGE AT SCAN	1.000	$F_{[3,85]}$= 0.0	1.000
GENDER	.971	$F_{[3,83]}$= 0.8	.486
IQ	**.918**	**$F_{[3,85]}$= 2.5**	**.062**
YEARS OF PARENTAL EDUCATION(Lower; Higher)	.963	$F_{[3,85]}$= 0.3	.967
HANDEDNESS	.995	$F_{[3,83]}$= 0.1	.940
SNR	.985	$F_{[3,85]}$= 0.4	.729

CAREGORICAL VARIABLES(PRIMARY HYPOTHESIS)	**Wilks' Lambda**	**STATS**	**Sig.**
Broader-diagnostic GROUP (Youth *with-Behav.;* Youth *with-Emot.;* Youth *with-Both)*	.843	$F_{[6,160]}$= 2.4	.032

DIMENTIONAL VARIABLES(SECONDARY HYPOTHESIS)	**Wilks' Lambda**	**STATS**	**Sig.**
PGBI-10M	.992	$F_{[3,85]}$= 0.2	.884
K-MRS	**.910**	**$F_{[3,85]}$= 2.8**	**.044**
K-DRS	.957	$F_{[3,85]}$= 1.3	.290
SCARED[a]	.999	$F_{[3,85]}$= 0.0	.993

Effect of MEDICATIONS	**Wilks' Lambda**	**STATS**	**Sig.**
STIMULANT MEDICATION	.913	$F_{[6,160]}$= 1.2	.290
NON-STIMULANT MEDICATION	.949	$F_{[6,160]}$= 0.7	.647
ANTIDEPRESSANT MEDICATION	.977	$F_{[6,160]}$= 0.3	.931
MOOD STABILIZER MEDICATION	.972	$F_{[6,160]}$= 0.4	.887
ANTIPSYCHOTIC MEDICATION	.943	$F_{[6,160]}$= 0.8	.572

SITE was covariate of no-interest in all the models

[a]Missing info in 4 LAMS youth

Table-2

Level-2 analyses. Multivariate Multiple Regression Analysis upon FA(w/o CONT)

Effect	Wilks' Lambda	STATS	Sig.
IQ	.941	$F_{[3,78]}$= 2.0	.126
K-MRS	.917	**$F_{[3,78]}$ = 2.3**	**.079**
Broader-diagnostic GROUP	.875	**$F_{[6,156]}$= 2.2**	**.047**

Level-3 analyses. **Univariate Multiple Regression Analysis upon FA(w/o CONT)**			
Effect	**RECONSTRUCTED TRACTS [FA]**	**STATS**	**Sig.**
IQ	FORCEPS MINOR	$F_{[1,80]}$= 2.6	.111
	CINGULUM	$F_{[1,80]}$= 0.0	.870
	UNCINATE FASCICLUS	$F_{[1,80]}$= 1.2	.280
K-MRS	FORCEPS MINOR	$F_{[1,80]}$= 0.3	.607
	CINGULUM	**$F_{[1,80]}$= 4.2**	**0.043** [a]
	UNCINATE FASCICLUS	= 0.2	.650
Broader-diagnostic GROUP	**FORCEPS MINOR**	**$F_{[2,80]}$= 3.3**	**.042**
	CINGULUM	$F_{[2,80]}$= 0.1	.872
	UNCINATE FASCICLUS	**$F_{[2,80]}$= 4.9**	**.009**

Level-4 analyses. **Post-hoc Pairwise Comparisons upon FA(w/o CONT)**				
RECONSTRUCTED TRACTS [FA]	**VS.**		**Mean Difference** [b]	**Sig.** [c]
FORCEPS MINOR	Youth *with-Emot.DD*	**Youth *with-Behav.DD***	***−0.037***	***.025***
		Youth *with-Both*	**−0.038**	**.015**
CINGULUM [d]	Youth *with-Emot.DD*	Youth *with-Behav.DD*	−0.005	.759
		Youth *with-Both*	−0.008	.611
UNCINATE FASCICLUS [e]	Youth *with-Emot.DD*	**Youth *with-Behav.DD***	**−0.043**	**.004**
		Youth *with-Both*	**−0.040**	**.004**

SITE was covariate of no-interest in all the models

[a] Parameter Estimates(Beta=0.188; t=2.1; p=0.043) showed a positive relationship between K-MRS and FA in the CINGULUM across all LAMS youth. Further between-group comparisons revealed trend-higher FA values(Mean Difference=0.031; Sig.P value=0.084) in LAMS youth with k-MRS>14 versus those with K-MRS<14 in the CINGULUM, after controlling for SITE and IQ.

[b] The mean difference is based on the estimated marginal means

[c] Adjustment for multiple comparisons in univariate and post-hoc analyses: Bonferroni(0.05/3=0.016; in bold). Trend levels of significance are >0.016 and ≤0.05(in italic bold).

[d] There was a main effect of laterality(F[1,80]=11.6;p=0.001), but there was no laterality by Broader-diagnostic GROUP interaction(F[2,80]=0.1;p=0.915) and no laterality by K-MRS interaction(F[1,80]=0.7;p=0.390) in the CINGULUM. FA was higher in the left CINGULUM than right CINGULUM across all participants.

[e] There was no effect of laterality(F[1,80]=0.4;p=0.538), no laterality by Broader-diagnostic GROUP interaction(F[2,80]=0.1;p=0.890) and no laterality by K-MRS interaction(F[1,80]=0.3;p=0.610) in the UNCINATE FASCICULUS.