Published in final edited form as:

Brain Imaging Behav. 2020 October ; 14(5): 1507–1520. doi:10.1007/s11682-019-00078-8.

White matter microstructure relates to lassitude but not diagnosis in adolescents with depression

Kathryn R. Cullen¹, Roland Brown², Melinda Westlund Schreiner³, Lynn E. Eberly², Bonnie Klimes-Dougan³, Kristina Reigstad¹, Dawson Hill¹, Kelvin O. Lim¹, Bryon A. Mueller¹

Kathryn R. Cullen: rega0026@umn.edu

¹Department of Psychiatry and Behavioral Sciences, School of Medicine, University of Minnesota, 2450 Riverside Avenue, Minneapolis, MN 55454, USA

²Division of Biostatistics, School of Public Health, University of Minnesota, Minneapolis, MN, USA

³Department of Psychology, College of Liberal Arts, Minneapolis, MN, USA

Abstract

The neurobiology of adolescent depression remains poorly understood. Initial studies suggested impaired white matter microstructure in adults and adolescents, but findings have not been consistent. Challenges in this literature have included small samples, medication confounds and inconsistent correction for type I error. This study addressed these issues in a new examination of fractional anisotropy (FA) in adolescents with major depressive disorder (MDD) using diffusion tensor imaging. We examined FA in 81 adolescents aged 12–19 (44 MDD [all unmedicated], 37 controls). We conducted logistic regression analyses to examine the odds of MDD versus control based on FA within standard white matter tracts that were delineated by probabilistic tractography. We also examined relationships between FA and disease severity (overall depression and dimensions of illness). Finally, we conducted a voxel-wise group comparison of FA. All analyses covaried for age, sex and socioeconomic status, and applied rigorous corrections for multiple testing. Logistic regression did not reveal significant associations between diagnosis and FA within white matter tracts defined by probabilistic tractography. Dimensional analyses revealed that greater lassitude was associated with higher FA in right cingulum bundle and bilateral corticospinal tracts, but with lower FA in right anterior thalamic radiation. Voxel-wise group comparisons of FA did not reveal significant group differences. The current findings do not support low FA as a neurobiological marker of adolescent depression. Dimensional results suggest that FA relates to lassitude but not overall depression. Given the clinical and neurobiological

Correspondence to: Kathryn R. Cullen, rega0026@umn.edu.

Electronic supplementary material The online version of this article (<https://doi.org/10.1007/s11682-019-00078-8>) contains supplementary material, which is available to authorized users.

Compliance with ethical standards The research was approved and monitored by the University of Minnesota Institutional Review Board, Human Research Protection Program. The informed consent process was completed with all participants before participation in the study. For those 18–19 years, participants completed consent on their own. For those 17 years of age and younger, participants provided assent while parents completed the consent. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Conflict of interest None of the authors have any conflicts of interest to declare.

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heterogeneity of depression, future work utilizing dimensional approaches may help elucidate the role of white matter microstructure in adolescent depression neurobiology.

Keywords

Adolescent; Depression; White matter; Diffusion tensor imaging; Fractional anisotropy

Introduction

Major depressive disorder (MDD) frequently emerges during the adolescent period and is associated with severe consequences including recurrence, chronic suffering, and suicide. During adolescence, substantial changes occur in both gray and white matter (Giedd et al. 1999) that may render adolescents more vulnerable to developing depression and other mental health problems (Paus et al. 2008). Recent decades have seen considerable progress in understanding the neural systems implicated in depression, but fewer studies have examined the depression-related circuitry in adolescents. Given the ongoing changes during adolescence, it is possible that the neural abnormalities in adolescents with MDD are different from those in adulthood. Because early and successful intervention holds tremendous potential for restoring healthy developmental trajectories and avoiding future suffering, a priority should be to better understand the neural underpinnings of depression in adolescence in order to develop targeted treatments.

Neurobiological research (primarily in adults) has increasingly suggested that MDD is a disorder of impaired connectivity within neural networks (Mulders et al. 2015). The anatomical substrate of connections within neural networks is made up of neuronal axons, which *en masse* are referred to as white matter. Diffusion weighted imaging (DWI) is a magnetic resonance imaging (MRI) technique that uses the diffusion properties of water within tissue to create contrast. Diffusion tensor imaging (DTI) is a commonly used model applied to DWI data which provides information about the structural integrity within white matter tracts. Fractional anisotropy (FA) is a commonly used metric derived from DTI ranging from 0 to 1 which reflects the limits upon diffusion of water within tissue; from higher levels of FA (closer to 1), researchers infer higher degrees of white matter organization. Different methods have been used to analyze DTI data. One approach is to conduct voxel-wise, between-group comparisons throughout the brain on FA. Following seminal publications documenting lower FA in MDD patients than in healthy patients (e.g. (Ma et al. 2007)), the field has emphasized the need to incorporate robust statistical correction for multiple testing in this research, which had not been incorporated in the early work. Another issue has been concerns about mis-registration of white matter across subjects and partial voluming. To address these latter issues, Smith and colleagues developed the method of Tract Based Spatial Statistics (TBSS), which incorporates a non-linear alignment across subjects, and creates a white matter skeleton within which the voxel-wise comparison is conducted (Smith et al. 2006). Probabilistic tractography is another approach for analyzing diffusion imaging data that delineates white matter tracts, which can then be used as regions of interest (ROIs) to extract key metrics such as FA, volume, length, and other metrics that describe white matter integrity within each tract.

Numerous studies of adult MDD have been published reporting results on group differences in FA (Sexton et al. 2009). As reviewed by Choi and colleagues, when robust corrections are used to correct for multiple testing, findings vary widely across studies, with many studies showing lower FA in patients compared to healthy controls (HC) (in disparate areas), but several studies where patients either showed no difference (Kieseppä et al. 2010; Abe et al. 2010; Cullen et al. 2010) or showed greater FA (Blood et al. 2010) than HC. In the largest study to date, Choi and colleagues used TBSS in a sample of 134 medication-free adults versus 54 healthy controls, and reported no significant differences in FA anywhere in the brain (Choi et al. 2014). Additionally, to examine the role of false positives being reported from smaller samples in the literature, they randomly selected smaller subsets of their sample, conducted 100 comparisons and found statistically significant differences in 10 of the comparisons, most of which involved the corpus callosum among other regions. This result suggested that many of the reported findings in the literature with smaller samples may represent false-positives.

Examination of white matter pathology specifically during the period of adolescence is important not only because adolescence represents a critical window of time for the emergence of depression, but also because of white matter changes that occur during this developmental period which can be captured by DTI (Giorgio et al. 2008). Furthermore, since the growth patterns of white matter development may vary across tracts (Lebel et al. 2012), it is important to consider any group differences in a given tract in developmental context. To date, a few DTI studies have published results on FA in adolescents with MDD. In the first study, our group used tractography to delineate the white matter connection between subgenual anterior cingulate cortex and the amygdala (a tract primarily comprised of the uncinate fasciculus), two regions highly implicated in depression, in a sample of 14 adolescents with MDD and 14 controls (Cullen et al. 2010). We found lower FA in this tract in the right hemisphere in the depressed group. We also conducted voxel-wise group comparisons of FA and found tentative evidence for lower FA in 10 voxel clusters throughout the brain, including in the uncinate fasciculus and cingulum bundle, but these findings did not withstand correction for multiple comparisons (Cullen et al. 2010). However, limitations of this first study included a small sample ($n = 28$), and the fact that most of the adolescents with MDD were taking medications. Subsequent studies of FA in adolescents with and without MDD have largely suggested that those with or at high risk for MDD have lower FA compared to controls (Bessette et al. 2013; Cheng et al. 2014; Huang et al. 2011; LeWinn et al. 2014). However, other studies found mixed results including findings of lower FA in adolescents with depression together with also finding regions with greater FA, including in the uncinate fasciculus (Aghajani et al. 2013; Henderson et al. 2013) and in the posterior cingulum/hippocampal area (Henderson et al. 2013). In summary, for these few, small studies published to date, characterized by small samples, a range of findings have been reported including no group differences (that withstand corrections), lower FA, and higher FA in specific white matter tracts in adolescents with MDD compared to controls. Thus, questions remain as to the validity, specificity, and replicability of the findings to date, and it is not clear whether impairments in white matter integrity (lower FA) truly represent a core feature of the pathophysiology of MDD in adolescents.

It is also possible that some variation in the results is attributable to the heterogeneity of symptoms that result in a diagnosis of MDD. Recent initiatives in the field of mental health research have emphasized the importance of dimensional approaches to examining the biological basis of mental disorders (NIMH, 2011). This movement acknowledges the limited ground that has been gained from traditional, categorically-driven analyses defined by existing diagnostic classifiers. Inconsistency in DTI findings to date may reflect the complex heterogeneity of depression, where among those diagnosed with MDD, certain individuals or groups of individuals have divergent neurobiological profiles, and may represent distinct, but heretofore poorly defined, subgroups. These considerations support the utility of considering dimensional approaches to identify more specific brain-behavior relationships in patients with depression.

The current study aimed to examine white matter integrity (as measured by FA) in a larger sample of unmedicated depressed adolescents. The current work focused on FA, with the goal of limiting multiple testing and seeking to replicate the key findings in the literature. We used two methods to analyze FA. First, in a refinement on our prior work, we utilized the FreeSurfer program TRACULA (TRActs Constrained by UnderLying Anatomy), an automated tool to conduct probabilistic tractography using individually-based, automatically defined anatomical landmarks. Based on the prevailing theory that neural circuit connectivity impairments underlie deficits in emotion-related processes in depression, we predicted that lower FA in tracts within fronto-limbic circuitry, such as the cingulum bundle and the uncinate fasciculus, would be associated with depression. Additionally, in line with NIMH's Research Domain Criteria (RDoC) that focuses on dimensional features of mental illness, we also examined the relationships between FA and depressive symptom severity and internalizing symptom dimensions. For both categorical and dimensional analyses with TRACULA data, we considered the possibility that abnormalities in multiple white matter tracts may simultaneously predict psychopathology (diagnosis or symptom dimensions). Thus, these analyses were constructed with the clinical measures as the outcome and the multiple tract FA measures as the predictors. Finally, we used a whole brain, voxel-wise approach for comparing FA between groups using TBSS. This analysis used the more traditional statistical approach in which FA in each voxel is the outcome variable, and clinical diagnosis is the predictor. We generally predicted that, like our previous study and others, adolescents with MDD would show lower FA than HC. We further predicted that, in contrast to our initial study but in line with Bessette and colleagues, with the voxel-wise analysis of FA in a larger sample we would be able to detect between-group differences in FA that would survive corrections for multiple testing. Based on strong evidence noted above that FA changes across adolescent development, we also tested whether group differences in FA might differ by age.

Method

Participants

Adolescents between the ages of 12 and 19 years with MDD and age- and gender-frequency-matched healthy adolescents were recruited to participate in the study. Methods of recruitment included community postings and clinical referrals from mental health services

at the University of Minnesota and the surrounding area. The Institutional Review Board at the University of Minnesota approved this study. Upon passing a phone screening process, participants were invited to an initial visit, which began with completing the informed consent process (consent was provided by parents for those 17 years of age and younger, and by the adolescent for those aged 18–19 years; assent was provided by adolescents aged 17 years and younger.)

Assessment

All participants completed the Kiddie Schedule for Affective Disorders and Schizophrenia-Present and Lifetime Version (KSADS-PL) (Kaufman et al. 1997), to identify Axis I disorders as defined by the DSM-IV-TR. If under 18, the adolescent and the legal guardian completed separate interviews. Interviews were conducted by a child/adolescent psychiatrist (Dr. Cullen), a clinical psychologist (Dr. Klimes-Dougan), or a trainee (graduate student level or higher) who was under the direct supervision of Drs. Cullen and Klimes-Dougan. DSMIV-TR diagnoses were established through a consensus meeting that incorporated data from both interviews, clinical rating scales, and, if available, medical records.

Dimensional indices of depression symptom severity included the well-validated, self-report, the Beck Depression Inventory II (BDI-II) (Beck et al. 1996) and the Children's Depression Rating Scale (CDRS-R) (Poznanski et al. 1985). Additionally, a dimensional index of internalizing symptoms, the Inventory of Depression and Anxiety Symptoms (IDAS) (Watson et al. 2007), a 64 item, self-report index was administered to participants. The IDAS provides a score for the following symptom dimensions: lassitude, insomnia, suicidality, appetite loss, appetite gain, ill temper, well-being, social anxiety, panic, and traumatic intrusion. Lassitude is defined as a condition of weariness or fatigue, and is characterized by lack of interest, energy, or spirit. In the IDAS, this dimension captures feeling exhausted, low in energy and sleepy, having difficulty getting going, and feeling worse in the morning, and therefore reflects a combination of apathy, fatigue, anhedonia, and melancholia. The IDAS also includes two broader scales: general depression (which contains items overlapping with several other IDAS scales) and dysphoria. Although there is limited research with this scale, Watson and colleagues conducted a series of studies that showed evidence that these scales define a single underlying factor and can be used with a range of high risk populations (Watson et al. 2007). The authors also provide evidence of reliability and validity, including internal consistency, short-term stability, and convergent/discriminant validity (Watson et al. 2007).

Participant age and sex were self-reported. An estimated intelligence quotient (IQ) was measured using the Wechsler Abbreviated Scale of Intelligence (Wechsler 1999). Information about parental education and type of employment was collected in order to calculate a measure of socioeconomic status (SES) based on Hollingshead Four-Factor Index (Hollingshead 1975).

Inclusion and exclusion criteria

Adolescents in the MDD group were eligible for inclusion if they had a primary diagnosis of MDD, and for this particular sample (to avoid potential confounds due to the presence of

medication) were not taking antidepressant medications for the past 2 months. (Note that the larger study included a smaller sample of adolescents with MDD who were taking medications that were excluded here; see Fig. 2). For the current sample, stimulant medications were permitted, but these participants did not take their stimulant medication on the day of the scan.) Adolescents in the control group were eligible if they had no evidence of a current or past Axis I diagnosis. Exclusion criteria for both groups included a history of mental retardation, the presence of a neurological or chronic medical condition, or meeting DSM-IV-TR criteria for pervasive developmental disorder, bipolar disorder, or psychotic disorder.

Neuroimaging acquisition

All neuroimaging procedures were conducted at the Center for Magnetic Resonance Research at the University of Minnesota on a Siemens Trio 3 Tesla MRI scanner (Erlangen, Germany). A T1-weighted scan was collected with the following parameters: TR = 2530 ms, TE = 3.65 ms, TI = 1100 ms, flip angle = 7 degrees, voxel size $1 \times 1 \times 1 \text{ mm}^3$, GRAPPA = 2 (5 min). A dual spin echo, single shot, diffusion weighted echo planar scan was collected with the following parameters: TR = 8600 ms, TE = 90 ms, FOV 256 mm, voxel size $2 \times 2 \times 2 \text{ mm}^3$, 64 slices, GRAPPA = 2, 30 non-collinear volumes with b value = 1000 s/mm^2 and 6 volumes with b = 0 s/mm^2 (5.5 min). The Siemens field map sequence was used which includes voxel parameters matching those of the DWI acquisition. This was collected for the purpose of correcting the DWI data for the geometric distortion caused by magnetic field inhomogeneities (2 min).

Imaging data processing and analysis

T1 processing—The FreeSurfer software package (<https://surfer.nmr.mgh.harvard.edu>) was applied to the T1 data, automatically dividing the entire brain into a standard set of labeled brain regions.

DWI preprocessing—Tools from the FSL package (<https://fsl.fmrib.ox.ac.uk/fsl/fslwiki>) were used to preprocess the DWI data. First, *eddy_correct* was used to correct for motion and eddy current-induced distortion in the DWI images. To estimate the level of motion within the DWI scan between subjects, the relative displacement from the previous volume across the DWI series was extracted from the *eddy_correct* log files and the root mean square displacement was computed for each subject. The eddy current and motion corrected DWI data were then corrected for geometric distortion using a field map image and the *FUGUE*. *DTIFIT* was applied to the preprocessed data to compute the diffusion tensor.

Tractography processing—The FreeSurfer program TRACULA (<https://surfer.nmr.mgh.harvard.edu/fswiki/Tracula>) was applied to the preprocessed DWI data to conduct global probabilistic tractography based on anatomical priors created in the FreeSurfer processing. White matter tracts based on the Johns Hopkins University atlas were created for each individual (see Fig. 1). These tracts include the corpus callosum forceps major and minor, anterior thalamic radiation (ATR); the cingulum bundle, divided into the superior and rostral portion within the cingulate gyrus (CCG) and the inferior and caudal “angular bundle” which projects to the parahippocampus in the temporal lobe (CAB); the

inferior longitudinal fasciculus (ILF); the superior longitudinal fasciculus, including the parietal portion (SLF-P) and the temporal portion (SLF-T); the corticospinal tract (CST); and the uncinate fasciculus. All of these tracts are bilateral except those of the corpus callosum. Mean FA weighted by track probability was extracted from each tract for each person for further statistical analyses.

TBSS processing—The preprocessed DWI data was entered into TBSS, a program in FSL (<http://fsl.fmrib.ox.ac.uk/fsl/fsl-4.1.9/tbss/index.html>). TBSS creates a single white matter skeleton for each subject that is aligned to that of a standard template.

Statistical analysis—Descriptive statistics were tabulated overall and by patient/control groups. These included the mean and standard deviation for continuous variables and frequency with percentage for categorical variables. For the analyses examining relationships between white matter microstructure and clinical outcomes (diagnosis and symptom domains), two general approaches were taken. For the TRACULA data analyses, we designed the analyses such that abnormalities in multiple tracts could simultaneously predict clinical (categorical and dimensional) outcomes. The primary analysis utilized logistic regression, with diagnostic group status as the binary outcome and FA in all tracts as multiple predictors. Secondary dimensional analyses within the patient group used a series of linear regression analyses to evaluate the effect of FA in all tracts on outcomes of symptom severity as measured by each of the BDI, CDRS, and IDAS scores. For all of the above analyses, separate models were fit for left and right hemispheres and were adjusted for sex, age, and SES. Secondary analyses within the patient group were additionally adjusted for co-morbid anxiety. *P* values were corrected for multiple testing within each hemisphere (across the multiple FA measures that were tested) using the Holm method. All analyses were conducted using R v3.5.1.

The second approach was to conduct a more traditional group comparison at the voxel level using the TBSS approach, with FA as the outcome variable and group diagnostic status as the predictor. Specifically, we conducted a voxel-wise analysis examining the effect of MDD diagnosis on FA at each voxel in the FA skeleton that was created through the TBSS processing described above using a general linear model with age, sex, and SES as covariates. Follow-up analyses included (a) a whole-brain group $\times$ age interaction analysis to determine whether the relationship between FA and age may differ between groups, and (b) examining whole-brain correlations between depression dimensions and FA. The latter analyses focused on total BDI scores, total CDRS scores and IDAS-Lassitude (the only of the IDAS scores which showed strong relationships with FA in the tractography analyses). These follow-up analyses included covariates for sex and SES. The permutation method *randomise* and threshold-free cluster enhancement (<http://fsl.fmrib.ox.ac.uk/fsl/fsl-4.1.9/randomise/index.html>) were used for family-wise error correction to account for multiple testing.

Results

Participants

As illustrated in Fig. 2, a total of 145 adolescents completed consent for this study; 132 completed the clinical evaluation procedure and 110 adolescents completed the MRI procedure. (Note: the consent process occurred directly before one or the other of these procedures; adolescents who had been diagnosed with MDD through University of Minnesota clinical services, referred to the study and who were planning to start medication as prescribed by their doctor were fast-tracked to have their scan as soon as possible to avoid delaying treatment. Therefore, some adolescents were scanned who were later excluded (see Fig. 2). Forty-four adolescents with MDD and thirty-seven healthy control (HC) were included in the final analyses for this paper. Reasons for exclusion included not meeting diagnostic criteria ($N = 13$), not completing a clinical interview ($N = 5$), taking antidepressant medication ($N = 17$), $IQ < 80$, and poor diffusion imaging quality ($N = 3$). Demographic and clinical information about the two groups are summarized in Table 1. As expected, the groups differed on most clinical measures. There were no group differences in age or sex. There was a trend for MDD having lower SES than HC ($p = 0.093$). The relationships among clinical measures (Pearson correlations between BDI and CDRS and all of the IDAS subscales) are displayed in Supplementary Table 1. Inter-relationships among the dimensions of psychopathology were generally as expected. Among the general measures of depression severity, IDAS general depression score was more highly correlated with BDI (both self-report measures) than with CDRS-R (a clinician-report measure). In the current sample, internal consistency for all IDAS scales was between .850 and .955.

Motion analysis

We found no group differences with respect to motion (see Supplementary Table 2). We also examined whether the motion values were related to FA, and found trend-level relationships in which a greater degree of relative motion was associated with lower FA in the left uncinate ($p = 0.05$) and the left ILF ($p = 0.07$). However, these relationships were not significant after correcting for multiple comparisons (see Supplementary Table 3a and b).

Tractography: Logistic regression examining whether DTI measures predict group status

Logistic regression results did not reveal strong associations between tract FA measures and group status (see Table 2). The strongest findings (which did not withstand multiple corrections) were that higher FA in the left and right CCG and in the left uncinate were associated with greater odds of having an MDD diagnosis.

Tractography: Linear regression examining whether DTI measures predict clinical severity

As shown in Table 3, linear regression results from analyses examining the relationship between DTI measures and overall depression severity as measured by the BDI and the CDRS total scores revealed no significant findings. For the linear regression examining the relationship between white matter tract FA and the various dimensions of internalizing symptom dimensions as measured by the IDAS, the only dimension that revealed significant findings (after correction for multiple comparisons) was lassitude. Higher lassitude scores

were associated with higher FA in the right CCG and in the left and right CST, but with lower FA in the right ATR. A graphical display of the significant findings shows the relationships between FA and Lassitude in these circuits in Fig. 3.

TBSS results

No differences were present between control and MDD groups that survived multiple testing adjustments. Within the MDD group, there were no significant correlations between FA and overall depression severity (e.g., BDI, CDRS) or internalizing symptom dimensions (including lassitude) that withstood corrections. No significant clusters resulted from the interaction test in the group-by-age analysis.

Discussion

In this study we examined white matter microstructure in unmedicated adolescents with MDD and age- and sex-matched healthy adolescents. Using two different approaches to characterize FA (voxel-wise and tract-wise), we did not find any significant relationships between FA and depression diagnosis or with FA and most other dimensions psychopathology. Our findings add to uncertainty in the field that white matter development may differ across depressed and healthy adolescents.

One of the challenges of the field has been that the findings have been mixed with regard to white matter development for adolescents experiencing depression. Several studies have suggested lower FA associated with depression in various brain white matter areas (Bessette et al. 2013; Cheng et al. 2014; Huang et al. 2011; LeWinn et al. 2014; Sexton et al. 2009) and others suggesting either null findings (Kieseppä et al. 2010; Abe et al. 2010; Cullen et al. 2010; Choi et al. 2014) or increased FA in specific areas (Blood et al. 2010; Aghajani et al. 2013). Notably, many prior studies were small, did not focus on adolescents, and did not incorporate robust corrections for multiple testing, which is critically important at this stage in the field to avoid over-valuation of spurious findings and confer greater confidence that corrected findings represent true circuit pathology. This study set out to address these limitations. Our categorical (MDD versus control) analyses did not reveal any findings that survived correction for multiple comparisons. Despite the growing evidence indicating abnormalities in functional connectivity in adolescent depression (Cullen et al. 2014; Henje et al. 2015; Connolly et al. 2013; Cullen et al. 2009; Gabbay et al. 2013), the current results raise the possibility that structural connectivity remains intact in adolescents with depression. Nevertheless, there remain some avenues that should be more fully examined in the future.

One avenue to examine more fully with a larger sample pertains to the marginal group differences showing that higher FA in bilateral CCG and uncinate fasciculus was associated with greater odds of being in the patient group. The cingulum bundle and the uncinate fasciculus are white matter tracts connecting limbic and prefrontal regions, that have been implicated by prior research in depression (Bracht et al. 2015), and are known to play a role in emotion regulation (Ghashghaei and Barbas 2002; Bürgel et al. 2006; Wager et al. 2008). Although previously we documented the opposite pattern, with lower FA in these tracts (Cullen et al. 2010), it is possible that the previously reported findings were not

generalizable, or that they reflected some unknown difference in the two populations studied, or that they could be attributed to the effects of medication, or that they were spurious results from a small sample.

Our examination of the relationships between FA and specific dimensions of depression substantiated the utility of studying features of depression and the RDoC initiative to examine mental disorders with dimensional approaches while providing some potential avenues for future research. Of note, there were a large range of symptom dimensions assessed including two indices of severity and twelve indices of internalizing pathology. Only one of the dimensions of internalizing symptoms was significant. Lassitude is defined as a condition of weariness or fatigue, and is characterized by lack of interest, energy, or spirit. In the IDAS, this dimension captures feeling exhausted, low energy and sleepiness, difficulty getting going, and feeling worse in the morning, and therefore reflects a combination of apathy, fatigue, anhedonia, and melancholia (Watson et al. 2007). The correlation results between lassitude and FA are somewhat complex in that several of the relationships consisted of a positive correlation (i.e. higher FA in bilateral CST and right CCG were associated with higher lassitude) while one of the relationships consisted of a negative correlation (i.e. lower FA in right ATR was associated with higher lassitude).

First, the positive relationship between lassitude and FA in the CCG is in keeping with our trend-level findings discussed above, in which a diagnosis of MDD was associated with greater FA in the CCG. In addition, a prior adolescent MDD study found that greater FA in the posterior cingulum bundle was associated with greater severity of anhedonia (Henderson et al. 2013). Given the overlap between the constructs of anhedonia and lassitude, together the studies suggest that greater structural connectivity within the cingulum bundle, a core conduit of the limbic system, may be a biological underpinning for the melancholic aspects of depression that involve low energy, fatigue and loss of interest.

Second, the positive relationship between lassitude and CST reported here adds to some prior work where increased FA of the bilateral CST was found among individuals with Parkinson's Disease, which often includes co-morbid depression and symptoms of lassitude (Chen et al. 2018; Friedman et al. 2007; Marsh, 2013). Given the role of the CST in voluntary motor movement, additional research investigating its relationship to constructs involving a reduction or slowing of completing tasks, such as lassitude, may be warranted. Taken together (our uncorrected diagnostic results, and the three positive relationships between lassitude and FA within CCG and CST tracts), these reports serve to question the idea that lower levels of FA would be always associated with greater pathology, and in fact in some cases it may be the opposite.

Finally, given the other findings in the study, the negative relationship between FA and lassitude is somewhat surprising. However, this finding is consistent with Henderson et al. (2013) who also found a negative relationship between FA in the ATR and anhedonia in adolescents with MDD (Henderson et al. 2013). The anterior thalamic radiation is a brain connection that extends from the thalamus to the frontal lobe. Having a strong connection between thalamus and frontal lobe may be critical for maintaining energy and interest.

Future research is warranted to better understand the divergent patterns of relationships between depression symptom severity and FA across different white matter tracts. Although some of the findings here were somewhat unexpected, other reports in the literature have described associations between higher FA and greater pathology. One prior study of unmedicated adolescents with MDD found greater FA in the uncinate fasciculus in patients compared to controls (Aghajani et al. 2013). Another study reported that although adults with MDD had lower FA in the parietal cortex than controls, higher FA in the thalamus was positively correlated with disease severity (Osoba et al. 2013). A third study reported that although adolescents with MDD showed lower FA in the posterior cingulum bundle (near the precuneus) than controls, they also showed higher FA than controls in the cingulum near the hippocampus (Henderson et al. 2013). As argued by Thomason and Thompson (2011), the psychiatric literature has maintained a misconception that higher FA is always consistent with better function, but “there may also be disease processes or developmental stages where higher FA—at the wrong place or the wrong time—is not beneficial to behavioral or other outcomes. Patients may concurrently have abnormally low or high FA in different brain regions” (Thomason and Thompson 2011) p. 77. Inconsistencies across studies could be related to study design limitations (results from small samples representing spurious findings, failure to correct for multiple tests) or could also reflect a true heterogeneity in the population, where some patients with MDD have abnormally high FA and others have abnormally low FA.

Limitations of the current study include a relatively small sample size. Although our sample was larger than prior reports of diffusion tensor imaging in adolescent depression, current thinking in the field suggests that even larger sample sizes and meta-analytic approaches are preferable to reduce the risk of false-positives. Larger sample sizes would also allow for targeted probing and more elaborated exploration of the dimensional constructs of depression potentially further legitimizing the shift from using categorical to dimensional theoretical models of depression and enhancing the richness of inquiry possible with more nuanced approaches to study. Conclusions regarding dimensional findings would be enhanced by the use of additional, alternative validated personality indexes of internalizing pathology (e.g., the Personality Assessment Inventory (Morey 2007)). While the IDAS has a strong theoretical basis, recent modifications (IDAS-II) (Watson et al. 2012) have further enhanced this instrument. It is possible that the construct of lassitude considered here is imprecise, and it remains unclear which specific aspects of lassitude are linked with white matter structure. Arguably, narrower features of fatigue, sleep problems, or apathy could be better suited to characterize this brain-behavior relationship. Indeed there are cross loadings on one item (slept more than usual) on the lassitude scale (Watson et al. 2007) suggesting that in future research it may be useful to include alternative sleep measures (e.g., the Pittsburgh Sleep Quality Index (Buysse et al. 1989)). Second, the cross-sectional nature of our study limits our ability to delineate neurodevelopmental trajectories in adolescents with depression in contrast to normative developmental processes. Studies of normative development have suggested that FA increases during adolescence and into early adulthood, and then decreases later in life (Lebel et al. 2012; Barnea-Goraly et al. 2005; Giorgio et al. 2008). In particular, the cingulum bundle and the uncinate fasciculus have been shown to undergo a prolonged developmental period with delayed declines in FA with age in

comparison to other white matter tracts (Lebel et al. 2012). Longitudinal studies, beginning before the onset of depression and comparing the trajectory FA changes in these tracts across childhood and adolescents in participants that develop versus those that do not develop depression (and between subgroups of patients), will be necessary to fully characterize the neurodevelopmental pathology of adolescent depression. Finally, while recent strides in neuroimaging have led to more advanced technologies, allowing for data acquisition with higher resolution, greater number of directions and reduced artifact (Urbil et al. 2013), these advances had not yet been available at the time that this study was initiated. It is possible that application of more modern technologies to examine FA in this same study population could have been more revealing.

In conclusion, in the current study of adolescents with unmedicated depression, we found limited evidence of association between FA in any white matter tracts and either depression diagnosis, depression severity, or clinical severity in any particular dimensions of depression, with the exception of lassitude. Our findings add to uncertainty in the field regarding the relationship between white matter development and adolescent depression, as defined as a categorical construct. However, our findings indicate that features of depression (lassitude) may be linked to DTL, lending credence to the importance of studying what is already accepted as a heterogeneous disorder with a dimensional conceptualization. This may ultimately be more useful to understanding the neurobiology of depression as it impacts the human condition, and provide first steps in the work of identifying the nature and organization of one of the dimensions of depression (Cuthbert 2005). In order to resolve this uncertainty and address these important questions, we propose several next steps for the field. First, large samples, and application of robust statistical approaches for type I error correction, should aid in the reduction of false positives and the revelation of “true” white matter pathology associated with depression. Further, incorporation of modern technologies such as multi-band imaging promises to optimize data quality, potentially allowing for increased sensitivity and reduction of false positives related to artifact (Urbil et al. 2013). Finally, it may be that abnormal FA in white matter tracts does not represent a core part of the pathophysiology of the depression diagnosis, but rather represents a vulnerability to develop specific problems that may be relevant to depression or features of depression, such as lassitude. In the spirit of current national initiatives that emphasize the need to examine brain-behavior relationships outside of the context of diagnosis, selection of broadly-defined subjects and collection of multi-dimensional clinical information should be incorporated into future studies. This would be a promising approach to better understand the heterogeneity of depression and how an individual’s profile of white matter microstructure may underlie their particular pattern of psychopathology.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Funding This study was funded by the National Institute of Mental Health (K23MH090421) and the National Alliance for Research on Depression.

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Fig. 1.

White matter tracts defined using TRACULA software in one person. TRACULA is an automated approach that uses a person's anatomical landmarks (as defined by the FreeSurfer software) to guide probabilistic tractography to define a set of standard, atlas-based white matter tracts for each person. **a** (Red) Corpus Callosum Forceps Major and Minor; **b** (Yellow) Left and Right Anterior Thalamic Radiation; **c** (Teal) Left and Right Cingulum-Cingulate Gyrus; **d** (Orange) Left and Right Inferior Longitudinal Fasciculus; **e** (Grey) Left and Right Superior Longitudinal Fasciculus-Parietal; **f** (Light Blue) Left and Right Superior Longitudinal Fasciculus-Temporal; **g** (Green) Left and Right Cingulum-Angular Bundle; **h** (Purple) Left and Right Corticospinal Tract; **i** (Blue/Indigo) Left and Right Uncinate Fasciculus

Fig. 2.
Consort Diagram. The flow of study participants and rates of completion through each phase of the study is shown

Fig. 3. Relationships between lassitude and fractional anisotropy in right CCG, right ATR, and bilateral CST. The line on each scatter plot shows the model-estimated relationship between the FA measure and lassitude, calculated for a person with characteristics equal to the mean value for all other variables in the model (sex, age, and SES)

Table 1

Demographics clinical measures overall and by diagnostic group

Covariate	Overall (N = 81)	Control (N = 37)	MDD (N = 44)
Male	58 (71.6%)	25 (67.6%)	33 (75.0%)
Parent SES	48.4 (12.1)	50.8 (11.6)	46.3 (12.3)
Age	16.1 (2.06)	16.3 (2.12)	15.9 (2.02)
IQ	108 (14.3)	110 (11.9)	106 (15.8)
Missing	7 (8.64%)	5 (13.5%)	2 (4.55%)
BDI Total Score	16.4 (15.2)	2.19 (2.68)	26.2 (12.2)
Missing	17 (21.0%)	11 (29.7%)	6 (13.6%)
CDRS Raw Score	58.4 (10.8)	25.0 (NA)	59.2 (9.57)
Missing	39 (48.1%)	36 (97.3%)	3 (6.82%)
IDAS General Score	43.8 (18.7)	28.5 (5.07)	57.5 (15.5)
IDAS Dysphoria	21.1 (10.4)	12.9 (3.51)	28.4 (9.05)
IDAS Lassitude	14.3 (6.38)	9.8 (3.13)	18.3 (5.84)
IDAS Insomnia	11.3 (5.43)	7.57 (1.96)	14.6 (5.42)
IDAS Suicidality	9.2 (5.14)	6.06 (0.24)	12.0 (5.78)
IDAS Appetite Loss	5.38 (3.15)	3.34 (1.24)	7.21 (3.24)
IDAS Appetite Gain	5.27 (2.86)	4.23 (1.7)	6.21 (3.35)
IDAS Ill Tempe	9.24 (5.09)	6.31 (2.0)	11.9 (5.59)
IDAS Weil-Being	21.7 (7.26)	26.7 (5.02)	17.1 (5.85)
IDAS Social Anxiety	9.49 (4.87)	6.49 (1.84)	12.2 (5.17)
IDAS Panic	11.4 (5.01)	8.74 (1.38)	13.9 (5.8)
IDAS Traumatic Intrusions	6.23 (3.3)	4.46 (1.2)	7.82 (3.76)
IDAS Scores Missing	7 (8.64%)	2 (5.41%)	5 (11.4%)
Medications at MRI Scan Any	15 (18.5%)	5 (13.5%)	10 (22.7%)
ADHD Stimulants	3 (3.7%)	0 (0.0%)	3 (6.8%)
Other *	12 (14.8%)	5 (13.5%)	7 (15.9%)
Comoro id Diagnoses Any			27 (61.4%)
General Anxiety Disorder			16 (36.4%)
ADHD			6 (13.6%)
Social Anxiety			6 (13.6%)
Specific Phobia			3 (6.8%)
Oppositional Defiant Disorder			2 (4.5%)
Panic Disorder			2 (4.5%)
PTSD			2 (4.5%)
Anorexia			1 (2.3%)
OCD			1 (2.3%)
Dysthymia			1 (2.3%)

Values presented are mean (SD) or N (%)

* Other medications include oral antibiotics (N = 5), oral birth control pills (N = 4), prilosec (N = 1), levothyroxine (N = 1), advair inhaler (N = 1)

Table 2

Logistic regression results. Outcome was depression or not

Hemisphere	Covariate	OR (95% CI)	P value	Adjusted P
Left	CCG (per 0.1 units)	7.52 (1.27, 44.36)	0.026	0.208
	CAB (per 0.1 units)	1.97 (0.43, 9.00)	0.379	1.000
	UNC (per 0.1 units)	14.13 (0.92, 216.14)	0.057	0.399
	ATR (per 0.1 units)	0.36 (0.03, 4.39)	0.426	1.000
	CST (per 0.1 units)	0.34 (0.03, 4.52)	0.413	1.000
	ILF (per 0.1 units)	0.18 (0.02, 1.71)	0.134	0.774
	SLFP (per 0.1 units)	14.16 (0.46, 433.42)	0.129	0.774
	SLFT (per 0.1 units)	0.16 (0.00, 7.36)	0.346	1.000
	CCG (per 0.1 units)	4.18 (0.94, 18.52)	0.060	0.479
	CAB (per 0.1 units)	1.62 (0.42, 6.28)	0.484	1.000
Right	UNC (per 0.1 units)	3.68 (0.29, 46.45)	0.313	1.000
CES = 0.224	ATR (per 0.1 units)	0.42 (0.02, 8.24)	0.569	1.000
CES _{adj} = -0.017	CST (per 0.1 units)	1.48 (0.15, 15.11)	0.739	1.000
	ILF (per 0.1 units)	0.48 (0.05, 4.80)	0.533	1.000
	SLFP (per 0.1 units)	0.37 (0.01, 9.00)	0.538	1.000
	SLFT (per 0.1 units)	5.48 (0.13, 234.56)	0.375	1.000

P value multiple comparison adjustment was done with the Holm method within each hemisphere. For each model, Cohen's modified effect size (CES) was calculated as $R^2_{ps}/(1-R^2_{ps})$, where R^2_{ps} is McFadden's pseudo R^2 calculated from the logistic regression models. An adjusted Cohen's effect size (CES_{adj}), adjusted for the number of covariates in the model and calculated using McFadden's adjusted pseudo- R^2 is also reported

FA, fractional anisotropy; MDD, major depressive disorder; CCG, cingulum bundle; CAB, cingulum angular bundle; UNC, uncinate fasciculus; ATR, anterior thalamic radiations; CST, corticospinal tract; ILF, inferior longitudinal fasciculus; SLFP, superior longitudinal fasciculus- parietal lobe; SLFT, superior longitudinal fasciculus-temporal lobe

Table 3

Linear Regression of survey outcomes on FA measures (per 0.1 units) in unmedicated depression

Outcome	Tract	Left Hemisphere Estimate (95% CI)	P value	Adjusted P	Right Hemisphere Estimate (95% CI)	P value	Adjusted P
BDI Total Score	CCG	3.97 (-8.78, 16.71)	0.542	1.000	0.72 (-12.11, 13.55)	0.913	1.000
	CAB	8.88 (-4.49, 22.24)	0.193	1.000	6.80 (-4.60, 18.21)	0.242	1.000
LH CES = 0.368	UNC	-6.91 (-36.19, 22.36)	0.644	1.000	4.49 (-18.47, 27.45)	0.701	1.000
LH CESadj = -0.043	ATR	-9.49 (-29.43, 10.44)	0.351	1.000	-17.21 (-41.19, 6.78)	0.160	1.000
	CST	7.57 (-12.51, 27.66)	0.460	1.000	17.97 (0.81, 35.13)	0.040	0.321
RH CES = 0.519	DLP	-4.00 (-23.95, 15.95)	0.694	1.000	-10.95 (-30.12, 8.21)	0.263	1.000
RH CESadj = 0.064	SLPP	20.37 (-9.60, 50.34)	0.183	1.000	-7.17 (-34.70, 20.37)	0.610	1.000
	SLPT	-6.02 (-37.36, 25.32)	0.707	1.000	3.34 (-25.61, 32.30)	0.821	1.000
CDRS Raw Score	CCG	-0.39 (-11.44, 10.66)	0.945	1.000	-4.14 (-15.60, 7.32)	0.479	1.000
	CAB	4.28 (-6.82, 15.39)	0.450	1.000	5.63 (-4.89, 16.15)	0.294	1.000
LH CES = 0.158	UNC	-12.61 (-35.86, 10.65)	0.288	1.000	-5.28 (-25.53, 14.97)	0.609	1.000
LH CESadj = -0.190	ATR	-3.64 (-21.78, 14.51)	0.694	1.000	-9.00 (-32.37, 14.37)	0.451	1.000
	CST	3.84 (-15.71, 23.40)	0.700	1.000	12.44 (-6.21, 31.09)	0.191	1.000
RH CES = 0.201	DLP	4.41 (-12.59, 21.41)	0.611	1.000	-5.10 (-22.58, 12.38)	0.567	1.000
RH CESadj = -0.159	SLPP	-11.97 (-37.60, 13.67)	0.360	1.000	10.98 (-13.03, 34.99)	0.370	1.000
	SLPT	17.41 (-10.34, 45.16)	0.219	1.000	4.50 (-20.37, 29.36)	0.723	1.000
IDAS General Score	CCG	6.36 (-10.97, 23.70)	0.472	1.000	-0.24 (-19.54, 19.05)	0.980	1.000
	CAB	0.14 (-16.57, 16.86)	0.986	1.000	0.02 (-16.53, 16.58)	0.998	1.000
LH CES = 0.405	UNC	-11.19 (-40.05, 17.67)	0.447	1.000	4.83 (-25.84, 35.51)	0.757	1.000
LH CESadj = -0.039	ATR	-6.68 (-34.26, 20.89)	0.635	1.000	-29.08 (-65.59, 7.42)	0.118	0.828
	CST	14.39 (-12.39, 41.18)	0.292	1.000	24.39 (3.07, 45.71)	0.025	0.200
RH CES = 0.610	DLP	4.45 (-23.49, 32.39)	0.755	1.000	4.05 (-24.87, 32.97)	0.784	1.000
RH CESadj = 0.102	SLPP	0.17 (-39.61, 39.94)	0.993	1.000	0.57 (-38.60, 39.73)	0.977	1.000
	SLPT	3.36 (-37.79, 44.52)	0.873	1.000	-6.60 (-41.94, 28.73)	0.714	1.000
IDAS Dysphoria	CCG	5.18 (-4.87, 15.24)	0.312	1.000	0.57 (-10.31, 11.45)	0.918	1.000
	CAB	1.04 (-8.66, 10.73)	0.834	1.000	-0.10 (-9.44, 9.23)	0.982	1.000
LH CES = 0.425	UNC	-5.81 (-22.55, 10.93)	0.497	1.000	4.47 (-12.82, 21.76)	0.613	1.000
LH CESadj = -0.025	ATR	-4.87 (-20.87, 11.13)	0.551	1.000	-19.72 (-40.30, 0.86)	0.060	0.422

Outcome	Tract	Left Hemisphere Estimate (95% CI)	P value	Adjusted P	Right Hemisphere Estimate (95% CI)	P value	Adjusted P
RH CES = 0.729	CST	8.32 (-7.22, 23.85)	0.294	1.000	15.04 (3.02, 27.06)	0.014	0.114
	DLP	2.46 (-13.75, 18.66)	0.766	1.000	4.75 (-11.55, 21.06)	0.568	1.000
	SLPP	-1.29 (-24.37, 21.78)	0.913	1.000	-2.59 (-24.67, 19.49)	0.818	1.000
RH CES _{adj} = 0.183	SLPT	0.00 (-23.88, 23.87)	1.000	1.000	-4.48 (-24.40, 15.44)	0.659	1.000
IDAS Lassitude	CCG	6.79 (1.73, 11.84)	0.008	0.059	8.48 (2.10, 14.86)	0.009	0.055
	CAB	-1.39 (-6.26, 3.49)	0.577	1.000	-0.08 (-5.55, 5.39)	0.976	1.000
	UNC	-3.34 (-11.75, 5.08)	0.437	1.000	-1.74 (-11.88, 8.39)	0.736	1.000
LH CES = 1.346	ATR	-2.53 (-10.57, 5.51)	0.537	1.000	-18.70 (-30.76, -6.64)	0.002	0.019
LH CES _{adj} = 0.605	CST	12.73 (4.92, 20.54)	0.001	0.011	10.61 (3.57, 17.66)	0.003	0.022
RH CES = 1.093	DLP	-7.98 (-16.13, 0.16)	0.055	0.329	1.09 (-8.47, 10.65)	0.823	1.000
	SLPP	-5.45 (-17.04, 6.15)	0.357	1.000	-10.03 (-22.98, 2.91)	0.129	0.643
	SLPT	4.04 (-7.96, 16.04)	0.509	1.000	6.63 (-5.05, 18.31)	0.266	1.000
IDAS Insomnia	CCG	-0.70 (-7.39, 5.99)	0.838	1.000	0.97 (-6.76, 8.70)	0.806	1.000
LH CES = 0.155	CAB	-2.85 (-9.31, 3.60)	0.386	1.000	-4.92 (-11.55, 1.71)	0.146	1.000
	UNC	-1.23 (-12.37, 9.91)	0.829	1.000	2.59 (-9.70, 14.88)	0.680	1.000
	ATR	3.40 (-7.24, 14.05)	0.531	1.000	-1.87 (-16.50, 12.75)	0.802	1.000
RH CES = 0.229	CST	5.85 (-4.49, 16.19)	0.268	1.000	3.35 (-5.19, 11.90)	0.442	1.000
	DLP	-2.55 (-13.34, 8.23)	0.643	1.000	6.62 (-4.97, 18.21)	0.263	1.000
	SLPP	-5.42 (-20.77, 9.94)	0.489	1.000	-7.24 (-22.94, 8.45)	0.366	1.000
RH CES _{adj} = -0.159	SLPT	4.78 (-11.11, 20.67)	0.555	1.000	-2.08 (-16.24, 12.08)	0.774	1.000
IDAS Suicidality	CCG	-2.02 (-8.51, 4.48)	0.543	1.000	-4.25 (-12.60, 4.09)	0.318	1.000
	CAB	0.65 (-5.61, 6.91)	0.838	1.000	-0.82 (-7.97, 6.34)	0.823	1.000
	UNC	-5.14 (-15.95, 5.67)	0.351	1.000	0.74 (-12.52, 14.00)	0.913	1.000
LH CES = 0.394	ATR	1.22 (-9.10, 11.55)	0.816	1.000	-0.58 (-16.36, 15.20)	0.942	1.000
LH CES _{adj} = -0.046	CST	-7.78 (-17.81, 2.25)	0.128	0.999	-0.78 (-10.00, 8.44)	0.868	1.000
RH CES = 0.198	DLP	2.60 (-7.86, 13.06)	0.626	1.000	3.00 (-9.51, 15.50)	0.639	1.000
	SLPP	11.66 (-3.23, 26.55)	0.125	0.999	4.79 (-12.15, 21.72)	0.580	1.000
	SLPT	-1.65 (-17.06, 13.76)	0.834	1.000	-6.84 (-22.12, 8.44)	0.380	1.000
IDAS Appetite Loss	CCG	0.44 (-3.57, 4.45)	0.831	1.000	1.96 (-2.63, 6.56)	0.402	1.000
LH CES = 0.148	CAB	-1.42 (-5.28, 2.45)	0.472	1.000	-1.58 (-5.52, 2.37)	0.434	1.000
	UNC	-0.83 (-7.50, 5.84)	0.807	1.000	3.39 (-3.92, 10.70)	0.363	1.000

Outcome	Tract	Left Hemisphere Estimate (95% CI)	P value	Adjusted P	Right Hemisphere Estimate (95% CI)	P value	Adjusted P
LH CESadj = -0.0215	ATR	-0.41 (-6.78, 5.97)	0.900	1.000	-6.71 (-15.41, 1.99)	0.130	1.000
	CST	3.50 (-2.70, 9.69)	0.268	1.000	2.14 (-2.94, 7.23)	0.408	1.000
RH CES = 0.238	DLP	1.74 (-4.72, 8.20)	0.597	1.000	1.19 (-5.70, 8.08)	0.735	1.000
	SLPP	-3.65 (-12.85, 5.54)	0.436	1.000	2.05 (-7.28, 11.39)	0.666	1.000
RH CESadj = -0.153	SLPT	1.77 (-7.74, 11.29)	0.715	1.000	-0.73 (-9.15, 7.70)	0.866	1.000
	CCG	1.87 (-1.69, 5.44)	0.303	1.000	4.05 (-0.31, 8.41)	0.069	0.421
IDAS Appetite Gain	CAB	0.08 (-3.35, 3.52)	0.961	1.000	-1.74 (-5.47, 2.00)	0.363	1.000
	UNC	-1.46 (-7.40, 4.48)	0.630	1.000	-3.06 (-9.98, 3.87)	0.387	1.000
LH CES = 0.552	ATR	1.68 (-3.99, 7.36)	0.560	1.000	1.19 (-7.05, 9.43)	0.777	1.000
LH CESadj = 0.062	CST	5.22 (-0.29, 10.73)	0.063	0.443	0.69 (-4.13, 5.50)	0.780	1.000
RH CES = 0.476	DLP	1.85 (-3.89, 7.60)	0.527	1.000	6.59 (0.06, 13.12)	0.048	0.383
	SLPP	1.08 (-7.10, 9.26)	0.796	1.000	-8.48 (-17.33, 0.36)	0.060	0.421
RH CESadj = 0.010	SLFT	-9.48 (-17.94, -1.01)	0.028	0.226	-2.62 (-10.60, 5.36)	0.520	1.000
	CCG	-0.39 (-6.44, 5.67)	0.901	1.000	1.10 (-6.06, 8.26)	0.763	1.000
IDAS Ill Temper	CAB	1.95 (-3.88, 7.79)	0.512	1.000	-1.85 (-8.00, 4.29)	0.554	1.000
LH CES = 0.502	UNC	3.93 (-6.15, 14.00)	0.445	1.000	-3.38 (-14.76, 8.00)	0.561	1.000
	ATR	-7.44 (-17.07, 2.18)	0.130	0.980	-6.24 (-19.78, 7.30)	0.366	1.000
RH CES = 0.525	CST	2.25 (-7.10, 11.60)	0.638	1.000	1.63 (-6.28, 9.54)	0.687	1.000
	ELF	-7.68 (-17.44, 2.07)	0.123	0.980	1.17 (-9.56, 11.90)	0.830	1.000
RH CESadj = 0.043	SLPP	1.76 (-12.12, 15.65)	0.804	1.000	-15.74 (-30.27, -1.21)	0.034	0.270
	SLPT	2.21 (-12.16, 16.58)	0.763	1.000	11.94 (-1.17, 25.05)	0.074	0.520
IDAS Well-Being	CCG	-0.38 (-6.96, 6.19)	0.909	1.000	6.65 (-0.67, 13.98)	0.075	0.525
	CAB	-1.07 (-7.41, 5.26)	0.740	1.000	-6.05 (-12.34, 0.23)	0.059	0.472
LH CES = 0.393	UNC	-3.71 (-14.65, 7.24)	0.507	1.000	2.20 (-9.44, 13.84)	0.711	1.000
	ATR	1.73 (-8.73, 12.19)	0.745	1.000	-3.88 (-17.73, 9.98)	0.583	1.000
RH CES = 0.594	CST	2.10 (-8.06, 12.26)	0.686	1.000	-6.06 (-14.16, 2.03)	0.142	0.710
	ELF	-0.25 (-10.85, 10.34)	0.962	1.000	8.80 (-2.17, 19.78)	0.116	0.696
RH CESadj = 0.091	SLPP	-8.87 (-23.96, 6.21)	0.249	1.000	-6.10 (-20.96, 8.77)	0.421	1.000
	SLPT	1.57 (-14.04, 17.17)	0.844	1.000	-2.77 (-16.18, 10.64)	0.686	1.000
IDAS Social Anxiety	CCG	0.27 (-4.98, 5.53)	0.919	1.000	0.38 (-5.84, 6.60)	0.905	1.000
	CAB	-4.86 (-9.93, 0.20)	0.060	0.479	-3.56 (-8.90, 1.78)	0.191	1.000

Outcome	Tract	Left Hemisphere Estimate (95% CI)	P value	Adjusted P	Right Hemisphere Estimate (95% CI)	P value	Adjusted P
LH CES = 0.704	UNC	-3.52 (-12.27, 5.22)	0.430	1.000	0.33 (-9.55, 10.22)	0.947	1.000
LH CESadj = 0.166	ATR	2.85 (-5.51, 11.20)	0.504	1.000	-8.59 (-20.36, 3.17)	0.152	1.000
	CST	4.88 (-3.23, 13.00)	0.238	1.000	6.44 (-0.43, 13.32)	0.066	0.529
RH CES = 0.725	ELF	1.22 (-7.25, 9.68)	0.778	1.000	6.33 (-2.99, 15.66)	0.183	1.000
RH CESadj = 0.180	SLPP	-9.06 (-21.11, 3.00)	0.141	0.985	-0.01 (-12.64, 12.61)	0.998	1.000
	SLPT	7.47 (-5.01, 19.94)	0.241	1.000	-2.25 (-13.64, 9.15)	0.699	1.000
IDAS Panic	CCG	2.21 (-4.14, 8.57)	0.494	1.000	3.98 (-3.22, 11.18)	0.279	1.000
	CAB	-3.47 (-9.59, 2.65)	0.267	1.000	-5.42 (-11.60, 0.76)	0.086	0.685
LH CES = 0.470	UNC	-2.32 (-12.89, 8.26)	0.668	1.000	1.72 (-9.72, 13.17)	0.768	1.000
LH CESadj = 0.006	ATR	-2.20 (-12.31, 7.90)	0.669	1.000	-9.92 (-23.54, 3.70)	0.153	0.920
	CST	7.15 (-2.66, 16.96)	0.153	1.000	6.51 (-1.45, 14.46)	0.109	0.763
RH CES = 0.623	ELF	0.85 (-9.39, 11.08)	0.871	1.000	5.72 (-5.07, 16.52)	0.299	1.000
RH CESadj = 0.111	SLPP	0.91 (-13.66, 15.49)	0.902	1.000	-2.97 (-17.59, 11.64)	0.690	1.000
	SLPT	-2.23 (-17.31, 12.84)	0.772	1.000	-5.64 (-18.83, 7.55)	0.402	1.000
IDAS Traum. Intrnl.	CCG	-0.47 (-4.83, 3.89)	0.833	1.000	-0.70 (-5.71, 4.30)	0.782	1.000
	CAB	-0.62 (-4.82, 3.58)	0.773	1.000	-2.50 (-6.79, 1.79)	0.253	1.000
LH CES = 0.311	UNC	1.15 (-6.10, 8.41)	0.755	1.000	3.76 (-4.19, 11.71)	0.354	1.000
LH CESadj = -0.103	ATR	-2.51 (-9.44, 4.42)	0.478	1.000	-5.64 (-15.10, 3.82)	0.243	1.000
	CST	2.49 (-4.24, 9.22)	0.468	1.000	2.67 (-2.86, 8.20)	0.344	1.000
RH CES = 0.413	ELF	0.17 (-6.85, 7.19)	0.962	1.000	3.86 (-3.64, 11.36)	0.313	1.000
RH CESadj = -0.033	SLPP	4.09 (-5.91, 14.09)	0.422	1.000	2.97 (-7.19, 13.12)	0.567	1.000
	SLPT	-0.95 (-11.29, 9.39)	0.857	1.000	-5.78 (-14.94, 3.38)	0.216	1.000

Hemisphere analyses conducted with separate models. Multiple testing adjustment used the Holm method within each model. For each model, Cohen's modified effect size (CES) was calculated as $R^2/(1-R^2)$. An adjusted Cohen's effect size (CESadj), adjusted for the number of covariates in the model and calculated using adjusted R^2 , is also reported

IDAS, Index of Depression and Anxiety Symptoms; MDD, major depressive disorder; CCG, cingulum bundle; CAB, cingulum angular bundle; UNC, uncinate fasciculus; ATR, anterior thalamic radiations; CST, corticospinal tract; ELF, inferior longitudinal fasciculus; SLFP, superior longitudinal fasciculus- parietal lobe; SLFT, superior longitudinal fasciculus- temporal lobe