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Publication Date

2022-08-01

DOI

10.1016/j.pscychresns.2022.111491

Peer reviewed

HHS Public Access

Author manuscript

*Psychiatry Res Neuroimaging*. Author manuscript; available in PMC 2023 August 01.

Published in final edited form as:

*Psychiatry Res Neuroimaging*. 2022 August ; 324: 111491. doi:10.1016/j.pscychresns.2022.111491.

# White matter integrity in adolescent irritability: A preliminary study

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## Abstract

Irritability is a prevalent, impairing transdiagnostic symptom, especially during adolescence, yet little is known about irritability's neural mechanisms. A few studies examined the integrity of white matter tracts that facilitate neural communication in irritability, but only with extreme, disorder-related symptom presentations. In this preliminary study, we used a group connectometry approach to identify white matter tracts correlated with transdiagnostic irritability in a community/clinic-based sample of 35 adolescents (mean age=14 years, SD=2.0). We found positive and negative associations with irritability in local white matter tract bundles including sections of the longitudinal fasciculus; frontoparietal, parolfactory, and parahippocampal cingulum; corticostriatal and thalamocortical radiations; and vertical occipital fasciculus. Our findings support functional neuroimaging studies that implicate widespread neural pathways, particularly emotion and reward networks, in irritability. Our findings of positive *and* negative associations reveal a complex picture of what is "good" white matter connectivity. By characterizing irritability's neural underpinnings, targeted interventions may be developed.

### Keywords

irritability; white matter; connectometry; adolescence; diffusion weighted

## 1. Introduction

Adolescence is a pivotal time for neurological development, particularly the ongoing process of neural pruning, and features major changes in white matter tracts as adolescents transition into young adulthood (Colby et al., 2013; Hagmann et al., 2010; Klingberg,

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**Declarations of interest**: none.

2008; Spear, 2013). Simultaneously, adolescents undergo profound changes in their psychosocial development and experience a dramatic uptick in psychiatric symptoms during this period (Casey et al., 2010). Prior studies have found associations between structural brain alterations, including white matter tissue integrity, and psychopathology throughout adolescence (Hamilton et al., 2008; Thomason & Thompson, 2011; van Velzen et al., 2020). Indeed, white matter (i.e., myelin) is critical for efficient communication between neurons and, when degraded, is associated with poorer mood and cognitive functioning (e.g., emotion regulation, working memory, inhibitory control, information processing speed; Eden et al., 2015; Fields, 2008; Magistro et al., 2015; Penke et al., 2012; Takeuchi et al., 2011; Zheng et al., 2018). Impairments in neurobehavioral functioning, such as inhibitory control, are in turn associated with increased vulnerability for a range of psychopathology (Perhamus & Ostrov, 2021), thus, providing further evidence of potential impacts of white matter degradation on psychiatric symptoms in youth.

More recently, investigations of transdiagnostic psychiatric symptoms (i.e., Research Domain Criteria research; Insel et al., 2010) have shown neural circuitry aberrations differ not only by diagnostic category, but across dimensions of behavioral domain criteria (Nielsen et al., 2021; Sabharwal et al., 2016; Stout et al., 2018). Irritability, defined as a lowered threshold to anger as compared to peers, is of transdiagnostic import, as it features in multiple psychiatric diagnoses (e.g., depressive, anxiety, bipolar, disruptive mood dysregulation, autism spectrum, and attention deficit hyperactivity disorders; Brotman et al., 2017; Leibenluft & Stoddard, 2013). Although some degree of irritability is normative in adolescence, clinically elevated levels are associated with impairment in adulthood, including increased risk for psychopathology (i.e., depression, anxiety, suicidality) and lower socioeconomic attainment (Dougherty et al., 2015; Elvin et al., 2021; Orri et al., 2019; Stringaris et al., 2009). Thus, irritability is a consequential transdiagnostic symptom dimension, with the potential for far-reaching advancement in the understanding and treatment of many different psychiatric disorders (Krieger et al., 2013; Leibenluft, 2017). Characterizing the neural underpinnings of irritability, including structural differences in white matter integrity, may prove valuable in identifying and targeting specific pathways for treatment.

Diffusion weighted imaging provides high-resolution images that are used to make inferences about white matter microstructural integrity. One more common index of white matter integrity computed from diffusion weighted imaging is fractional anisotropy, which is thought to relate to the degree of white matter tissue tract coherence and myelination across fiber bundles. In clinical neuroscience, decreased fractional anisotropy has been shown in many psychiatric diagnoses with irritability features, including depressive (Chen et al., 2021; van Velzen et al., 2020), bipolar (Brown et al., 2021), generalized anxiety (Liao et al., 2014), attention deficit hyperactivity (Hamilton et al., 2008), autism spectrum (Shukla et al., 2011), and disruptive mood dysregulation (Linke et al., 2020) disorders. Despite these findings with diagnostic categories, far fewer studies have examined the relationship between youth brain microstructure and transdiagnostic symptoms such as irritability.

Prior examinations of neural mechanisms of irritability have primarily focused on functional activity in response to functional MRI tasks or during rest, implicating prefrontal and

temporal regions associated with reward and emotion regulation (Dougherty et al., 2018; Hodgdon et al., 2021; Kryza-Lacombe et al., 2021; Nielsen et al., 2021; Wiggins et al., 2016); yet, valuable insights about potential structural differences in neural circuitry remain underexplored. To date, there have only been three studies examining diffusion-weighted brain images with respect to irritability (Gregory et al., 2015; Henderson et al., 2013; Linke et al., 2020). Gregory et al., (2015) found that adults with Huntington's disease who reported higher levels of irritability showed less structural integrity across nearly all white matter tracts across the entire brain. Another study (Henderson et al., 2013) observed increased irritability levels in adolescents with major depressive disorder were associated with decreased integrity in prefrontal-striatal white matter tracts as well as within the occipital cortex and near the amygdala. More recently, irritability investigated transdiagnostically across youths with disruptive mood dysregulation or bipolar disorders and healthy volunteers was associated with weakened white matter integrity in centralized structures (e.g., corpus callosum and corticospinal tract; Linke et al., 2020). Taken together, there is budding evidence of abnormal white matter integrity in individuals with irritability-related disorders; however, prior studies primarily focused on irritability within specific diagnostic categories (or in the case of Linke et al., 2020, across extreme psychiatric presentations). As such, this line of investigation is still vastly underdeveloped, particularly for the range of irritability (low to moderately high) seen typically in the community.

Given the prior literature, the current preliminary study aims to identify irritability-related alterations in white matter integrity in adolescents recruited from the community by referrals from an anxiety/depression clinic, with varying degrees of irritability-related psychopathology symptoms commonly seen in the community. We predict a negative relationship between white matter integrity and irritability, measured dimensionally, in tracts connecting prefrontal and temporal, and parietal regions associated with reward and emotion regulation (Deveney et al., 2013; Hodgdon et al., 2021; Kryza-Lacombe et al., 2021; Scheinost et al., 2021; Tseng et al., 2019; Wiggins et al., 2016).

## 2. Methods

### 2.1. Participants

Data were collected from N=45 adolescents (mean age=13.97 years, SD=1.95; n=30 recruited from the community and enriched for clinical symptoms commonly seen in the community, n=15 referred from a local research clinic conducting a randomized controlled trial for a brief behavioral intervention for anxiety and depression). Distributions of irritability levels overlapped between the recruitment sources (see Supplemental Materials Table S2), and additional analyses were conducted to determine if recruitment source were primarily driving findings (see Results: Additional Analyses). Youths were excluded from participation if they or their parent/guardian reported MRI contraindications (e.g., metal implants, dental braces, weight >300 lbs., claustrophobia), any major medical problems with clear impact on the youth's central nervous system, and/or if youth were unable to understand procedures sufficiently to provide assent, based on a qualified research team member's assessment. Informed consent or assent were obtained from youth participants. Permission was obtained from a parent or guardian of participants younger than 18 years

old. Procedures were approved by the University of California San Diego Institutional Review Board and accepted by joint agreement by the San Diego State University Institutional Review Board. Data from ten participants were excluded due to incomplete MR data acquisition (n=4), issues with image reconstruction or dropout (n=3), or errors in sequence parameters (i.e., inconsistent b-values; n=3), resulting in a final sample of N=35 youths.

### 2.2. Irritability Measures

Irritability was measured using the Affective Reactivity Index (ARI; Stringaris et al., 2012). The dimensional irritability score from the ARI is comprised of six symptom items (Cronbach's alpha = .84). Respondents chose among "1=not true", "2=somewhat true", and "3=certainly true" for each item. The total score is generated by summing the scores of the six symptom items, with higher scores indicating more severe irritability symptoms. The ARI has excellent psychometric properties and has been validated in adolescents across multiple contexts (Dougherty et al., 2020; Evans et al., 2020). Both youth self-report and parent-report (on youth) versions of ARI were collected, but given recent work suggesting that youth self-report and parent report ARI measure potentially different constructs and the former has a vantage for reporting affective states in adolescents (Dougherty et al., 2020), we conducted the primary analysis using the youth self-report ARI. Analyses using parent-report ARI generated largely similar patterns and are presented in the Supplement.

### 2.3. Neuroimaging acquisition

Brain images were acquired using a 3.0T General Electric Discovery MR750 scanner with a Nova Medical 32-channel head coil. Participants were acclimated to MRI procedures in a mock scanner prior to scanning. Diffusion-weighted images were acquired using a single-shot multi-shell EPI sequence with 98 diffusion directions, six b=0 frames, and two b-values of 500 and 1000 at 46 directions each (TR=4000ms; TE=89). Two diffusion images were collected using reverse phase-encoded blips (A>P, P>A) to mitigate opposite-direction distortions. A field map scan was included to correct for $B_0$ distortion. Additionally, a high-resolution T1-weighted magnetization prepared rapid gradient echo sequence with prospective motion correction was used for alignment (MPRAGE PROMO; TR=4.94s; TE=1.988ms; TI=1060ms; slice thickness=1.0mm; voxel size=1.0mm$^3$; matrix=256×256mm; flip angle=8°; FOV=25.6).

### 2.4. Neuroimaging processing

After acquisition, reverse phase-encoded diffusion-weighted image pairs were combined into a single image to correct for susceptibility-induced off-resonance field and eddy current distortions using FSL's TOPUP function (Andersson et al., 2003; Smith et al., 2004). Eddy current distortion correction and standard space registration were completed with FSL's Diffusion Toolbox (FDT; Andersson & Sotiropoulos, 2016). Further processing was conducted with DSI Studio (F. Yeh, 2021) to prepare for correlational tractography (i.e., connectometry) analyses. To estimate the spin distribution function directly from the diffusion data, images were reconstructed in the Montreal Neurological Institute (MNI) space through q-space diffeomorphic reconstruction with a diffusion length ratio of 1.25 (F.-C. Yeh et al., 2010; F.-C. Yeh & Tseng, 2011). Goodness-of-fit was assessed with an

$R^2$ statistic between each participant's quantitative anisotropy (QA) map and MNI QA; a cutoff of $R^2$>.5 was used for quality assurance based on DSI developer recommendations and previous studies (Mojtahed Zadeh et al., 2018; F.-C. Yeh & Tseng, 2011; Zhuang et al., 2021). Generalized fractional anisotropy, calculated using the orientation distribution function, was chosen as the principal white matter microstructure index because it improves anisotropy measurement of areas with multiple diffusion directions (i.e., crossing fibers; Tuch, 2004). Like traditional fractional anisotropy estimates, greater generalized fractional anisotropy is associated with better white matter integrity (Tuch, 2004).

### 2.5. Statistical analyses

To examine the relationship between while matter tract integrity and irritability, we used DSI Studio (F. Yeh, 2021) to conduct group connectometry analyses. Connectometry is a measure of correlational tractography where fundamental units of the fiber structure, defined as local connectomes, are regressed with variables of interest to determine the association between the variable and white matter tract integrity. DSI Studio calculates the strength of neural connectivity within local connectomes based on density diffusing spins between proximal voxels within individual white matter tracts (F.-C. Yeh et al., 2016). Generalized fractional anisotropy values within local connectomes are then correlated with our study variable of interest, youth-reported irritability, and permutated to obtain the false discovery rates (FDRs) of resulting significant white matter tracts. Four iterations of topology-informed pruning and 4000 randomized permutations on the length of coherent associations were used (F.-C. Yeh et al., 2016). The connectometry analysis was run with minimum tract length 20 voxels (40mm) and a T-score threshold of 2, as prior studies have done (Hula et al., 2020; Olvet et al., 2016; F.-C. Yeh et al., 2013, 2016). To account for potential rank order effects with the irritability scale, Spearman partial correlation was used to determine the association between irritability and white matter integrity, with age and gender as covariates. Coherent bundles for significant positive and negative correlations were separated manually and identified by tract name using DSI Studio's tract recognition tool. As an illustrative analysis to determine direction of effects, mean generalized fractional anisotropy values were extracted for each participant and post-hoc Spearman correlations were conducted in SPSS (Version 28), with FDR correction for each tract bundle. We chose DSI Studio for better inclusion of all tracts and to reduce Type II error compared to TBSS methods. For full transparency, we report all results received from DSI Studio.

## 3. Results

### 3.1. Participants

Our sample included 35 children and adolescents aged 11–19 years ($M$=14.11, SD=1.90) and the majority were female (57.14%). The racial makeup of the sample was 54.29% White, 22.86% Biracial, 8.57% African American/Black, 2.86% Asian/Pacific Islander, while 11.43% indicated Other; 12 participants (34.29%) identified as Hispanic/Latino/a/x. The mean for youth-reported irritability was 2.74 (SD=2.60), which is above the established clinical cutoff of 2 (Kircanski et al., 2017; Stringaris et al., 2012). All demographic information is presented in Table 1.

### 3.2. Connectometry Results

Connectometry analyses revealed several tracts whose generalized fractional anisotropy values were positively correlated with youth irritability symptoms (FDR=0.013; examples presented in Figure 1), including tracts connecting multiple cortical regions, i.e., left superior longitudinal fasciculus in the subsection of the paracingulate fascicle, right inferior longitudinal fasciculus, bilateral frontoparietal, and bilateral parolfactory cingulum. Tracts that connected basal ganglia/limbic and cortical regions, including bilateral superior corticostriatal, right superior and posterior thalamocortical radiations, and right lateral parahippocampal; posterior tracts, including the dorsal portion of the right vertical occipital fasciculus, left cerebellum, corticospinal medial lemniscus; as well as tracts associated with sensory processing, including acoustic and optic radiations, were also positively correlated with irritability severity.

However, other tracts, as well as different regions within some of the same tracts that were positively correlated, showed a negative correlation between generalized fractional anisotropy and youth irritability severity (FDR=0.046; examples presented in Figure 2). Indeed, cortico-cortical tracts, including the dorsal portion of the left superior and right superior longitudinal fasciculus, dorsal bilateral frontal-parietal, left dorsolateral and medial-ventral parahippocampal and right medial ventral parahippocampal and anterior left parolfactory cingulum, were negatively correlated with irritability symptoms. Some portions of tracts connecting basal ganglia/limbic regions with cortex, including right anterior and left superior corticostriatal and left posterior thalamic radiation, were negatively correlated with irritability, as were visual regions, i.e., left cranial nerve II, right optic radiation tracts, and bilateral vertical occipital fasciculus, and posterior regions, i.e., bilateral cerebellum and middle cerebellar peduncle. FDR for each tract bundle is reported in Table 2.

All irritability-related tracts are presented in Supplemental Figures, both positively correlated tract (Figure S1) and negatively correlated tracts (Figure S2). Additional analyses (see Supplemental Materials Table S3) suggested that these correlations were not primarily driven by age, gender, recruitment source, or co-occurring anxiety or depression symptoms.

## 4. Discussion

The present study represents a novel investigation of white matter integrity alterations related to irritability in youths from the community. Overall, the connectometry analyses identified several white matter tracts that were correlated with youth-reported irritability, including both positive and negative associations. The few prior studies, which primarily focused on irritability in the context of a particular disorder (e.g., Huntington's disease, depression, bipolar, and disruptive mood dysregulation disorders; Gregory et al., 2015; Henderson et al., 2013; Linke et al., 2020) or extreme, disorder-related presentations of irritability (Linke et al., 2020), solely identified negative correlations between irritability and white matter integrity as measured by fractional anisotropy. By contrast, our findings, which evaluated individual differences in brain structures from a transdiagnostic perspective, including a spectrum of irritability severity typically seen in the community, suggest a more complex picture (both negative *and* positive correlations). Indeed, our findings of both positive and negative correlations demonstrate that greater fractional anisotropy values

may not always be “better” – at least in terms of irritability severity. This new nuance to the current understanding of structural connectivity in irritability parallels a similar evolution in the autism literature: whereas autism was once characterized as a disorder of underconnectivity (e.g., Just et al., 2004), multiple studies subsequently implicating overconnectivity in addition (e.g., Monk et al., 2010) showed that greater connectivity may not always be “better.” Rather than greater or lesser connectivity, maintaining a delicate balance within and among networks may be the mark of mental health (Picci et al., 2016).

Consistent with prior white matter studies (Gregory et al., 2015; Henderson et al., 2013; Linke et al., 2020), we observed that irritability was associated with widespread alterations in white matter integrity across broad swaths of the brain (e.g., longitudinal facisculi, corticospinal, posterior thalamic radiation, and inferior fronto-occipital) during this key adolescence period. These widespread alterations highlight the foundational nature of irritability neural mechanisms and may explain in part why irritability is involved in an array of psychiatric disorders and moreover has far-reaching, life-span consequences (e.g., detrimental mental health and socioeconomic outcomes; Dougherty et al., 2015; Elvin et al., 2021; Orri et al., 2019; Stringaris et al., 2009). Deviations from the typical trajectories of structural tissue development during this window of neural development may have profound impacts on optimal psychological functioning (Arain et al., 2013; Ashtari et al., 2007; Blakemore & Choudhury, 2006; Ziegler et al., 2019). Whereas DSI is not a direct measure of biological changes in white matter, these diffusion alterations may reflect degradation of white matter and thus, impaired communication among neurons. This in turn, may contribute to the altered activation and functional connectivity in irritability. Given the importance of white matter tracts for neurochemical communication in brain circuitry, this study emphasizes the transdiagnostic and foundational importance of youth irritability.

Overall, our connectometry findings implicated tracts connecting reward, emotion, and emotion regulation regions that have been identified in prior activation and functional connectivity work on irritability (Dougherty et al., 2018; Hodgdon et al., 2021; Kryza-Lacombe et al., 2021; Nielsen et al., 2021; Scheinost et al., 2021; Tseng et al., 2019; Wiggins et al., 2016). First, we found that irritability was associated with anterior, midcingulate and parahippocampal cingulum tracts, all of which have essential connections from the limbic center to the prefrontal cortex (Bubb et al., 2018; Heilbronner & Haber, 2014). Irritability-related neural circuits, (e.g., reward processing), align with the anterior and midcingulate cingulum regions (Dougherty et al., 2018; Hodgdon et al., 2021; Kryza-Lacombe et al., 2021). Further, alterations in anterior cingulum tracts demonstrate involvement of these tracts in a variety of psychiatric symptoms associated with anxiety, depression and obsessive-compulsive disorders (Bubb et al., 2018). Second, similar to limbic system, we found both superior and anterior corticostriatal tract differences related to irritability. The corticostriatal circuit undergoes significant changes during adolescence, marking developmental maturation of reward-based learning and inhibition (Chahal et al., 2021; Chen et al., 2021; Larsen et al., 2018). Investigations of functionality of the corticostriatal tracts reveal affective, reward and cognitive control network connections (Cox & Witten, 2019; Larsen et al., 2018), which map on to neural underpinnings of irritability (Brotman et al., 2017; Hodgdon et al., 2021; Kryza-Lacombe et al., 2021). Third, our findings of longitudinal fasciculus and frontoparietal tract involvement in irritability may

reflect the connection between the frontal and parietal lobes that had previously been seen in functional imaging studies (Scheinost et al., 2021; Tseng et al., 2019; Wiggins et al., 2016). Although these regions are responsible for an array of functions, these findings are consistent with prior work implicating motor control (Scheinost et al., 2021; Tseng et al., 2019) and face emotion recognition/mentalizing (Rich et al., 2008; Wiggins et al., 2016) as processes disrupted in irritability. Altogether, our microstructural findings bolster prior functional imaging work uncovering the psychological processes, such as reward and emotion regulation, related to irritability.

This study had several limitations. First, due to the modest sample, this investigation of white matter microstructure is preliminary. Second, although additional analyses suggested that age, gender, and recruitment source were not primarily driving our findings, such potential confounds cannot be ruled out. Third, as irritability is associated with other neural alterations such as cortical volume (Besteher et al., 2017; Dennis et al., 2019), this may be a confound despite normalization to a common template. This work documenting white matter integrity alterations in irritability sets the stage for follow-on research to investigate the relationship between gray and white matter changes in irritability. Lastly, clinical presentations are often complex. Although we focused on levels of irritability typically seen in the community by recruiting from community organizations and psychology clinics focusing on internalizing problems, and additional analyses suggested the involvement of irritability above and beyond depression and anxiety symptoms, other co-occurring symptoms may come into play. Additional research with larger samples, narrower age ranges, and varied clinical presentations will be needed to address the limitations of the current study.

Irritability is a pervasive and often impairing experience for many youths and has transdiagnostic import. Our findings help to explicate the neural pathways involved in irritability, bolstering prior work implicating widespread neural dysfunction, especially in regions associated with reward and emotion regulation and moreover suggesting that a complex pattern of over- and underconnectivity may mark irritability during the key adolescent developmental period. Such work will be foundational to elucidate the etiology of irritability and lay the groundwork for therapies that address these neural mechanisms.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## Funding:

This work was supported by the Brain & Behavior Foundation NARSAD Young Investigator Award [grant number: 26802] and UC San Diego ACTRI Pilot Projects from NIH Clinical and Translational Science Awards Program [grant number UL1TR001442]

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## Highlights

- Transdiagnostic irritability involves reward and emotion neural networks
- Connectometry analyses reveal widespread irritability-related tract associations
- White matter integrity is positively and negatively correlated with irritability

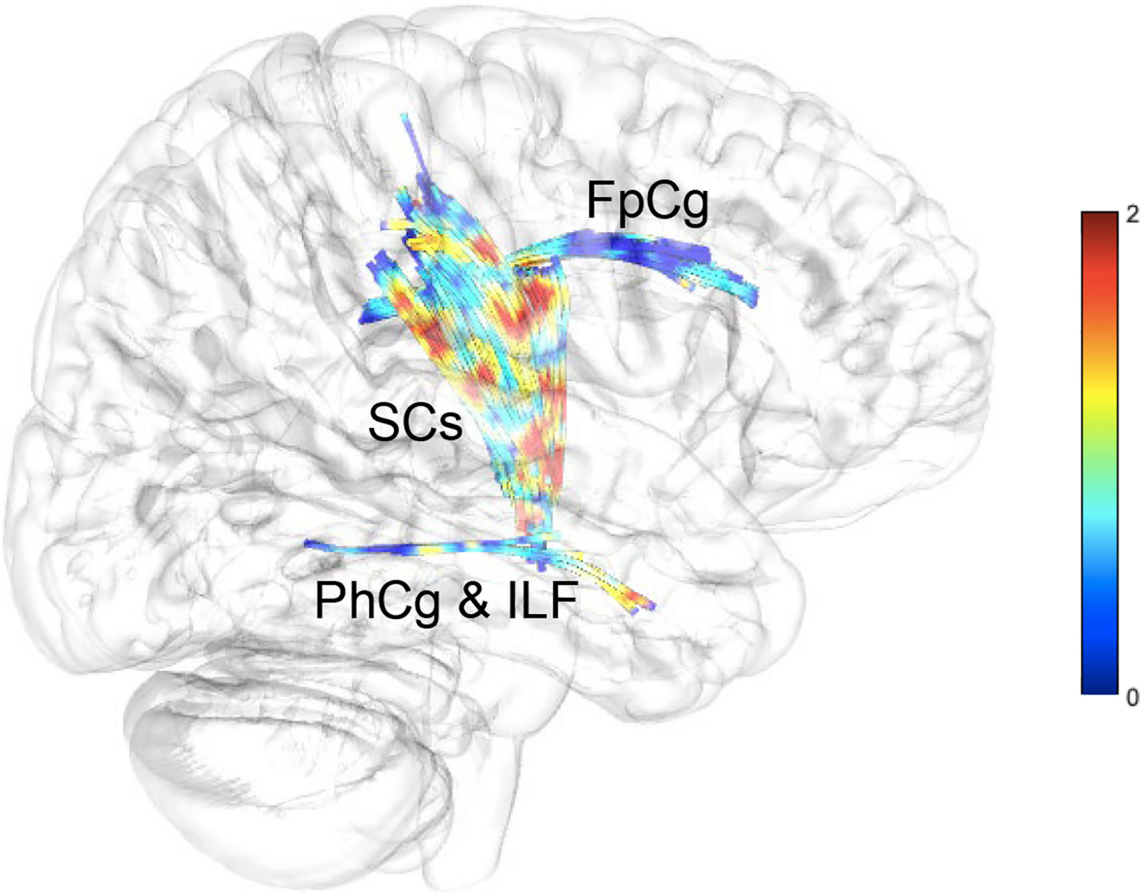


**Figure 1.**

Three white matter tract bundle examples that are positively correlated with youth-reported irritability (t-threshold=2). All tract bundles are located in the right hemisphere. Abbreviations: FpCg=Frontoparietal Cingulum; SCs=Superior Corticostriatal; PhCg=Parahippocampal Cingulum; ILF=Inferior Longitudinal Fasciculus.

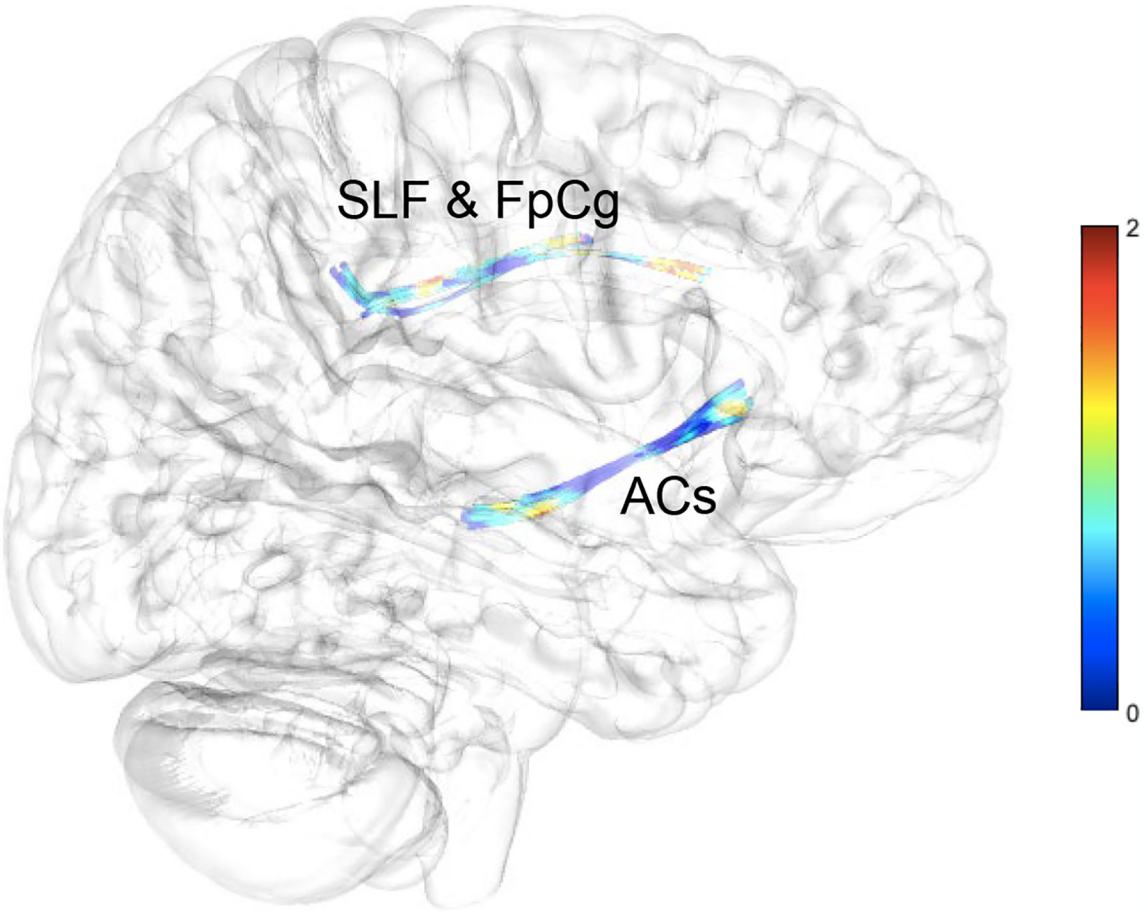


**Figure 2.**

Two white matter tract bundle examples that are negatively correlated with youth-reported irritability(t-threshold=2). The superior longitudinal fasciculus and frontoparietal cingulum tract bundle is located in the left hemisphere and the anterior corticostriatal tract bundle is in the right hemisphere. Abbreviations: FpCg=Frontoparietal Cingulum; SLF=Superior Longitudinal Fasciculus; ACs=Anterior Corticostriatal.

**Table 1.**

Sample Characteristics

| **Total N** | **35** | |
|---|---|---|
| | **%** | **n** |
| Female | 57.14 | 20 |
| Race | | |
| African American/Black | 8.57 | 3 |
| Asian/Pacific Islander | 2.86 | 1 |
| White | 54.29 | 19 |
| Biracial | 22.86 | 8 |
| Other | 11.43 | 4 |
| Ethnicity | | |
| Hispanic/Latinx | 34.29 | 12 |
| Medication Use | 25.71 | 9 |
| Household monthly income (*M* (SD)) | 7480.19 (6002.98) | |

| | ***M*** | **SD** | **Range** |
|---|---|---|---|
| Age | 14.11 | 1.90 | 11 – 19 |
| Irritability Symptoms (ARI; Youth report on self) | 2.74 | 2.60 | 0 – 10 |

Note: N=sample size; *M*=mean; SD=standard deviation ARI=Affective Reactivity Index

**Table 2.**

False Discovery Rates for Positive and Negative Correlated Tract Bundles (t-threshold=2)

| Bundle Regions | Number of Tracts | Mean Length (mm) | FDR |
|---|---|---|---|
| *Positively Correlated Tracts* | | | |
| Right Parahippocampal Cingulum, Right Inferior Longitudinal Fasciculus | 10 | 42.205 | 0.017 |
| Right Superior Corticostriatal, Right Superior Thalamic Radiation, Right Acoustic Radiation | 815 | 43.798 | 0.017 |
| Right Optic Radiation, Right Posterior Thalamic Radiation, Right Acoustic Radiation | 30 | 42.539 | 0.017 |
| Right Posterior Thalamic Radiation, Right Vertical Occipital Fasciculus | 149 | 43.342 | 0.017 |
| Right Posterior Thalamic Radiation, Right Vertical Occipital Fasciculus | 4 | 43.028 | 0.017 |
| Right Frontal Parietal Cingulum, Right Parolfactory Cingulum | 287 | 47.191 | 0.015 |
| Left Superior Longitudinal Fasciculus, Bilateral Frontal Parietal Cingulum, Left Parolfactory Cingulum | 122 | 43.676 | 0.017 |
| Left Superior Thalamic Radiation, Left Superior Corticostriatal | 22 | 42.375 | 0.017 |
| Left Superior Longitudinal Fasciculus | 2 | 45.015 | 0.017 |
| Left Cerebellum | 1 | 40.067 | 0.013 |
| *Negatively Correlated Tracts* | | | |
| Middle Cerebellar Peduncle | 61 | 42.338 | 0.057 |
| Right Parahippocampal Cingulum | 5 | 41.615 | 0.046 |
| Right Vertical Occipital Fasciculus, Right Optic Radiation | 41 | 44.691 | 0.070 |
| Right Anterior Corticostriatal | 29 | 43.937 | 0.057 |
| Left Superior Corticostriatal | 3 | 42.668 | 0.057 |
| Right Cerebellum | 52 | 41.537 | 0.046 |
| Left CNII | 5 | 44.390 | 0.070 |
| Left Parahippocampal Cingulum, Left Cerebellum | 81 | 42.179 | 0.057 |
| Left Parahippocampal Cingulum, Left Superior Corticostriatal | 50 | 43.653 | 0.057 |
| Left Vertical Occipital Fasciculus, Left Posterior Thalamic Radiation, Left Cerebellum | 219 | 45.077 | 0.070 |
| Left Posterior Thalamic Radiation | 6 | 44.344 | 0.070 |
| Left Superior Longitudinal Fasciculus, Bilateral Frontal Parietal Cingulum | 30 | 43.550 | 0.057 |
| Left Parolfactory Cingulum | 3 | 41.340 | 0.046 |
| Right Frontal Parietal Cingulum, Right Superior Longitudinal Fasciculus | 234 | 44.443 | 0.070 |
| Middle Cerebellar Peduncle, Right Inferior Cerebellar Peduncle | 13 | 43.701 | 0.057 |