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Structural atrophy of the right superior frontal gyrus in adolescents with severe irritability

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Abstract

Severe irritability is common in youths with psychiatric disorders and results in significant dysfunction across domains (academic, social, and familial). Prior structural MRI studies in the pediatric population demonstrated that aberrations of cortical thickness (CT) and gray matter volume (GMV) in the fronto-striatal-temporal regions which have been associated with irritability. However, the directions of the correlations between structural alteration and irritability in the individual indices were not consistent. Thus, we aim to address this by implementing comprehensive assessments of CT, GMV, and local gyrification index (LGI) simultaneously in youths with severe levels of irritability by voxel-based morphometry and surface-based morphometry. One hundred and eight adolescents (46 youths with severe irritability and 62 healthy youths, average age = 14.08 years, standard deviation = 2.36) were scanned with a T1-weighted MRI sequence. The severity of irritability was measured using the affective reactivity index. In youths with severe irritability, there was decreased CT, GMV, and LGI in the right superior frontal gyrus (SFG) compared to healthy youths, and negative correlations between these indices of the SFG and irritability. Our findings suggest that structural deficits in the SFG, potentially related to its role in inhibitory control, may be critical for the neurobiology of irritability.

KEYWORDS
cortical thickness, gray matter volume, gyrification, insula, superior frontal gyrus, superior temporal gyrus

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; ANCOVA, analysis of covariance; ARI, affective reactivity index; CAT, computational anatomy toolbox; CD, conduct disorder; CSA, cortical surface area; CT, cortical thickness; DARTEL, diffeomorphic anatomical registration through exponentiated lie algebra; DLPFC, dorsolateral prefrontal cortex; DMDD, disruptive mood dysregulation disorder; FOV, field of view; GLM, general linear model; GMV, gray matter volume; K-SADS, kiddie-schedule for affective disorders and schizophrenia for school-age children-present and lifetime version; LGI, local gyrification index; MANCOVA, multivariate analysis of covariance; MNI, Montreal neurological institute; MRI, magnetic resonance imaging; ODD, oppositional defiant disorder; pre-SMA, pre-supplementary motor area; SBM, surface based morphometry; SFG, superior frontal gyrus; SIG, severe irritability group; TC, temporal cortex; TE, echo time; TIV, total intracranial volume; TR, repetition time; VBM, voxel based morphometry; WASI, Wechsler abbreviated scale of intelligence.

1 | INTRODUCTION

Irritability is defined as a chronically excessive sensitivity to negative emotional stimuli and impaired behavioral control resulting in anger outbursts and reactive aggression (Beauchaine & Tackett, 2020; Leibenluft, 2017; Leibenluft, Blair, Charney, & Pine, 2003). Irritability manifests across various psychiatric disorders but is a cardinal dimensional psychopathology in disruptive mood and behavior disorders, such as attention-deficit/hyperactivity disorder (ADHD), oppositional defiant disorder (ODD), conduct disorder (CD), and disruptive mood dysregulation disorder (DMDD) (Avenevoli, Blader, & Leibenluft, 2015) .

The neurobiological mechanism of irritability in the pediatric population has been investigated mainly via neuroimaging modalities, such as functional and anatomical magnetic resonance imaging (MRI) (Adleman et al., 2012; Dennis, Humphreys, King, Thompson, & Gotlib, 2019; Deveney et al., 2012; Deveney et al., 2013; Gold et al., 2016; Jirsaraie et al., 2019; Pagliaccio, Pine, Barch, Luby, & Leibenluft, 2018; Singh et al., 2010; Stoddard et al., 2017; Tseng et al., 2019; Wiggins et al., 2016). In those studies, irritability has shown associations with functional and anatomical impairment within neural regions implicated in response inhibition/top-down attention control and affective regulation. Studies using functional MRI (fMRI) have reported that youths with severe irritability showed aberrant activation in neural areas implicated in emotion regulation, reward processing and motor execution: the amygdala, dorsolateral prefrontal cortex (DLPFC), striatum, and anterior temporal cortex (TC) (Crum et al., 2020; Deveney et al., 2012; Deveney et al., 2013; Gold et al., 2016; Singh et al., 2010; Stoddard et al., 2017; Tseng et al., 2019; Wiggins et al., 2016).

In the structural MRI studies, aberrations in cortical thickness (CT) and gray matter volume (GMV) have been associated with irritability (Adleman et al., 2012; Dennis et al., 2019; Gold et al., 2016; Jirsaraie et al., 2019; Pagliaccio et al., 2018). In these studies, irritability was associated with the aberrations of GMV in the regions relevant to emotion regulation and response inhibition/top-down attention control, such as the superior frontal gyrus (SFG) including pre-supplementary motor area (pre-SMA), DLPFC, TC, insula, and striatum. A recurrent finding in both CT and GMV is structural alteration in the SFG in youths with severe irritability (Adleman et al., 2012; Dennis et al., 2019; Gold et al., 2016; Pagliaccio et al., 2018). However, the relationship between irritability and structural alteration is unclear with conflicting results (Adleman et al., 2012; Dennis et al., 2019; Gold et al., 2016; Jirsaraie et al., 2019; Pagliaccio et al., 2018). While the studies measuring CT reported a positive relationship between irritability and the SFG thickness (Jirsaraie et al., 2019; Pagliaccio et al., 2018), the studies using GMV showed a negative relationship between irritability and SFG volume (Adleman et al., 2012; Dennis et al., 2019; Gold et al., 2016).

One potential explanation of this inconsistency is that GMV may reflect several structural parameters including not only CT associated with the laminar structure of the cortex (Hutton, Draganski, Ashburner, & Weiskopf, 2009; Panizzon et al., 2009), but also cortical surface area (CSA) relevant to the number of cellular columns (Rakic, 1988, 2007; Winkler et al., 2010) and gyrification related to the pattern of cortical folding which can be measured by local gyrification index (LGI) (Kelly et al., 2013; Schaer et al., 2008). Thus, there is a convincing rationale to investigate these properties (CT and GMV) as independent indices of brain structure simultaneously. Until now there was no research combining CT, GMV, and LGI together to investigate a fine-grained characterization of structural aberrations related to irritability, which is the main aim of this study.

To assess these indices, we employ the two most commonly used methods, voxel based morphometry (VBM) and Surface Based Morphometry (SBM). VBM and SBM are complementary methods for the observation of brain morphometry (Hutton et al., 2009). VBM provides the voxel wise estimation of the local amount or volume of a specific tissue compartment and is often used to investigate the local distribution of GMV (Ashburner & Friston, 2000). Surface-based morphometry techniques allow us to analyze additional brain features including CT (Fischl & Dale, 2000), CSA (Dale, Fischl, & Sereno, 1999), and LGI (Schaer et al., 2008). Although CSA is an index of brain volumetry, there is concern regarding high false positive rate of CSA (twice as high as that of CT) (Greve & Fischl, 2018). Thus, we decided to focus on CT, GMV, and LGI.

In short, the aim of this study is to investigate the relations between severe irritability and CT, GMV and LGI using VBM and SBM methods. We recruited a group of youths with diagnoses of Disruptive Behavior and Mood Disorders (ADHD, CD, ODD, and DMDD) and with severe irritability, and compared them with typically developing youths. Based on previous findings (Adleman et al., 2012; Dennis et al., 2019; Gold et al., 2016; Jirsaraie et al., 2019; Pagliaccio et al., 2018), we hypothesize; (1) The youths with severe irritability will have reduction of the fronto-striatal-temporal volumes in the GMV analysis. (2) Specifically, in the SFG, the youths with severe irritability will show increased CT as well as decreased GMV and LGI compared to typically developing youths.

2 | MATERIALS AND METHODS

2.1 | Participants

One-hundred eight participants participated in this study (age range 10–18, mean age = 14.08 ± 2.36). Participants were divided into two groups: (1) severe irritability group (SIG): youths with clinically significant level of irritability as defined by a score of 4 or greater (≥4) on the self-reported affective reactivity index (ARI) (Stringaris et al., 2012) ($N = 46$; 12 female; see Table 1 for details on their psychiatric diagnoses); and (2) control group (CG): typically developing youths ($N = 62$; 20 female). Written informed consent was obtained from all participants and their guardians. The guardians reviewed the consent documents and provided written permission. The Institutional Review Boards at the participating institutions approved this study.

Youths in the severe irritability group and their guardians were recruited from the outpatient clinic of a large academic medical center in the Midwest and the surrounding community. They were

TABLE 1 Demographic and clinical characteristics of the DMDD and healthy control groups

		Severe irritability group ($N = 46$)	Control group ($N = 62$)	*t* or chi
Sex	(Boy)	34 (73.91%)	42 (67.74%)	0.48
Age		13.78	14.32	1.2
IQ		100.45	102.97	1.33
ARI-S		6.52	1.02	16.73***
ARI-P		8.22	0.45	23.75***
TIV		1,486.22 (153.61)	1,494.97 (139.63)	0.31
Disorder	ADHD	38 (82.61%)	—	
	ODD	28 (60.87%)	—	
	MDD	10 (21.74%)	—	
	DMDD	22 (47.83%)	—	
	CD	5 (10.86%)	—	
	GAD	8 (17.39%)	—	

Abbreviations: ADHD, attention deficit hyperactivity disorder; ARI-S, self-report affective reactivity index; ARI-P, parent-report affective reactivity index; CD, conduct disorder; DMDD, disruptive mood dysregulation disorder; GAD, generalized anxiety disorder; ODD, oppositional defiant disorder.
***$p < .001$ for group comparisons.

interviewed by a licensed and board-certified child and adolescent psychiatrist and/or advanced practice psychiatric nurse using the Kiddie-Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS) (Kaufman et al., 1997) to confirm their psychiatric diagnoses.

The exclusion criteria were: (1) comorbid psychotic, tic, or substance abuse disorders, (2) autism spectrum disorder with associated significant impairments in communication and significant behavioral disturbance, (3) history of CNS disease (i.e., history of seizure, epilepsy, CNS tumor, and CNS Hemorrhage) or serious CNS infection (i.e., meningitis or encephalitis), (4) current user of anxiolytics (benzodiazepines), (5) positive urine pregnancy test, (6) positive urine drug screen, (7) metal in body, claustrophobia, or any other condition that would preclude MRI, or (8) intellectual disability (Wechsler Abbreviated Scale of Intelligence scores <70) (Wechsler, 2011). Current use of psychotropic medications (stimulants, alpha-agonists, antipsychotics, antidepressants, and mood stabilizers) was not exclusionary if the dose and schedule were stable for at least 6 weeks.

The healthy youths were recruited from community via advertisements to the participating research institution. Absence of clinical diagnoses was determined by a licensed and board-certified child and adolescent psychiatrist according to DSM-5 criteria (American Psychiatric Association, 2013).

2.2 | Measures

2.2.1 | Sociodemographic information

Participants and their guardians provided the participants' demographic characteristics upon enrollment, including age, sex, and ethnicity.

2.2.2 | Measures

The severity of irritability was measured using the Affective Reactivity Index (ARI) (Stringaris et al., 2012). The ARI is a reliable and valid instrument for assessing irritability and emotion dysregulation (test–retest correlation coefficient: 0.80 and Cronbach alpha = 0.92) (Mulraney, Melvin, & Tonge, 2014; Stringaris et al., 2012). The ARI comprises 7-item parallel parent- and self- reports that are designed to assess the child's irritable behavior (6 items; e.g., easily annoyed by others, often loses temper) and impairment (1 item; i.e., irritability causes problems) over the past 6 months. Ratings were made based on a 3-point Likert scale, ranging from 0 (Not true) to 2 (Certainly true).

IQ was measured by the Wechsler Abbreviated Scale of Intelligence (WASI-I or II) to rule out intellectual disability (IQ < 70) (Wechsler, 2011).

2.3 | Data acquisition

Neuroimaging data were collected on a 3T Siemens Skyra scanner (Erlangen, Germany). A T1-weighted magnetization-prepared rapid gradient-echo sequence was used for obtaining high-resolution anatomical images with the following parameters: 176 axial slices, repetition time (TR) = 2,200 ms; echo time (TE) = 2.48 ms; flip angle = 8°; field of view (FOV) = 23×23 cm^2; matrix = 256×208; slice thickness = 1 mm; voxel size = $0.9 \times 0.9 \times 1$ mm^3.

Quality control was conducted at multiple points in the data processing; first, the raw T1-weighted images were visually examined for structural abnormalities and artifacts (e.g., ghosting or blurring) due to head motion or dental instruments (prior to preprocessing), secondly, the statistical quality checks were performed using covariance between normalized segmented images to assess inter-subject homogeneity and overall image quality and identify possible outliers

(i.e., gray matter segmented images with mean values greater than two standard deviations from the sample mean), and a visual inspection of the final preprocessed image was conducted again for potential newly introduced artifacts. No participant was excluded following these steps.

2.4 | Voxel-based morphometry (VBM) analysis

2.4.1 | Preprocessing of VBM

VBM analysis was performed using the Computational Anatomy Toolbox (CAT12; http://dbm.neuro.uni-jena.de/cat/), an extension toolkit of the Statistical Parametric Mapping software package (SPM12, https://www.fil.ion.ucl.ac.uk/spm/software/spm12/) running in MATLAB (R2019a; MathWorks, Natick, MA). CAT12 provides the platform for all the analyses including voxel-based morphometry as well as surface-based morphometry, and it offers processing pipelines for both procedures. Prior research confirmed the accuracy of CAT12 as a measurement of CT (Dahnke, Yotter, & Gaser, 2013) and folding index (Righart et al., 2017; Seiger, Ganger, Kranz, Hahn, & Lanzenberger, 2018).

All anatomical images were preprocessed as follows: (1) correcting for bias-field inhomogeneity; (2) segmenting into gray matter, white matter, and cerebrospinal fluid (Ashburner & Friston, 2005); (3) creating the customized gray matter templates from the study images using the diffeomorphic nonlinear registration algorithm (diffeomorphic anatomical registration through exponentiated lie algebra, DARTEL) technique to improve inter-subject brain image registration (Ashburner, 2007); (4) warping the gray matter DARTEL templates into the tissue probability maps in Montreal Neurological Institute (MNI) space using registration and spatial normalization with preservation of the relative amount of GMV; (5) smoothing with an a 8-mm full width at half maximum (FWHM) Gaussian kernel for statistical analyses (Leblanc, Dégeilh, Daneault, Beauchamp, & Bernier, 2017).

2.4.2 | Brain tissue volumes: group analysis

After preprocessing, multivariate analysis of covariance (MANCOVA) was performed to determine contributions of group toward whole GMV, white matter, and CSF volumes controlling the nuisance variables including total intracranial volume (TIV), sex, IQ, and age using SPSS version 26 (IBM Corp., Armonk, NY).

2.4.3 | GMV: group analysis

Exploratory whole-brain VBM analysis for GMV was conducted to compare voxel-wise GMV difference between youths with severe irritability and healthy youths. To eliminate the edge effects between the gray and white matter border, all voxel with gray mater values of 0.1 (absolute threshold masking) were excluded. To control the effect of nuisance variables, age, TIV, IQ, and sex variables were entered as covariates.

2.4.4 | GMV: the severity of irritability within the youths with severe irritability

Partial correlation analysis was performed to investigate the association between GMV and the severity of irritability using ARI score after excluding the effect of the nuisance variables in youths with severe irritability. The statistical significance of group differences and correlation analysis were set at uncorrected $p < .001$ at a cluster extent of >50 voxels.

2.5 | Surface-based morphometry (SBM) analysis

2.5.1 | Preprocessing of SBM

Data preprocessing, cortical surface extraction, and statistical analyses were conducted with the CAT12 implemented in SPM12. We applied a fully automated processing pipeline for SBM provided by CAT12 toolbox that allows the simultaneous estimation of multiple morphometric parameters including CT and LGI based on the absolute means curvature approach (Luders et al., 2006) and the reconstruction of the central surface of the left and right hemisphere by using the projection-based thickness method (Dahnke et al., 2013).

SBM preprocessing involved the following steps: (1) estimating WM distance based on tissue segmentation, projection of local maxima to other GM voxels with a neighbor relationship derived by WM distance using partial volume correction, sulcal blurring, and sulcal asymmetries without sulcus reconstruction, (2) topological correcting using spherical harmonics-based approach (Yotter, Nenadic, Ziegler, Thompson, & Gaser, 2011), (3) spherical registration by applying an adapted volume-based diffeomorphic DARTEL algorithm, (4) reparameterization by the surfaces into a common coordinate system, (5) smoothing with a 15 mm (FWHM) (Dahnke et al., 2013; Leblanc et al., 2017).

Also, the LGI can be extracted based on an absolute mean curvature approach (Luders et al., 2006). Central cortical surfaces were created for both hemispheres separately.

2.5.2 | Mean CT in whole brain: group analysis

After preprocessing, analysis of covariance (ANCOVA) was performed to determine contributions of group toward mean CT of whole brain controlling for age, IQ, and sex covariates using SPSS version 26 (IBM Corp., Armonk, NY USA).

2.5.3 | CT and LGI: group analysis

Statistical comparisons were performed by applying the general linear model (GLM) approach implemented in CAT12/SPM12 for each of the two morphometric methods (i.e., LGI and CT). We conducted group difference of CT and LGI between youths with severe irritability and healthy youths using age, sex, and IQ as covariates. The threshold

of the statistical parametric map was at uncorrected $p < .001$ at a cluster extent of >50 voxels (Lee, Kwak, & Chey, 2019). Atlas labeling was performed according to Destrieux atlas (Destrieux, Fischl, Dale, & Halgren, 2010).

2.5.4 | CT and LGI: the severity of irritability within the patients with severe irritability

We performed whole-brain analyses investigating both positive and negative correlations between the severity of irritability and anatomical marker (i.e., CT and LGI) controlling the nuisance variables, applying thresholds of uncorrected $p < .001$ at a cluster extent of >50 voxels.

3 | RESULTS

3.1 | Participant characteristics

Individuals with severe irritability and healthy controls did not differ significantly in age ($t = 0.48$, $p = .63$), sex ($x^2 = 0.48$, $p = .49$), IQ ($t = 1.20$, $p = .23$), and TIV ($t = 0.31$, $p = .76$); see Table 1.

3.2 | VBM analysis

3.2.1 | Brain tissue volumes: group analysis

MANCOVA showed a significant main effect of group [$F(1, 106) = 3.664$, $p = .015$] for GM, WM, and CSF volumes after controlling TIV, age, IQ, and sex. Pairwise comparisons revealed that individuals with severe irritability had less total cortical GM [$F(1, 106) = 8.649$, $p = .004$] and larger WM volume [$F(1, 106) = 5.049$, $p = .027$] compared to healthy controls; see Table S1.

3.2.2 | GMV: group analysis and the severity of irritability within patients with severe irritability

In the group analysis, the severe irritability group had lower GMV in the bilateral superior/middle frontal gyrus, the bilateral insula, and putamen, left temporal gyrus, right parahippocampal gyrus, left middle occipital gyrus, left lingual gyrus, left angular gyrus, and right cerebellum compared to the healthy group. Also, there were significant negative correlations between the severity of irritability (i.e., ARI scores) and the GMV in right superior frontal gyrus (partial $r = -.49$), left precentral gyrus (partial $r = -.53$), left middle occipital gyrus (partial $r = -.35$), right parahippocampal gyrus (partial $r = -.47$), right cerebellum (partial $r = -.47$), and right caudate (partial $r = -.49$) within patients with severe irritability; see Table S2 and 2 and Figure 1. For the correlation result of the entire group, see Supplemental Material Section 1.

3.3 | SBM analysis

3.3.1 | Mean CT in whole brain: group analysis

There is no main effect of group [$F(1, 106) = .389$, $p > .05$] for mean CT after controlling IQ, age, and sex; see Table S1.

3.3.2 | CT: group analysis and the severity of irritability within the patients with severe irritability

In contrast to predictions but in line with the VBM analysis, the result of SBM group comparison showed decreased CT for the severe irritability group in the superior frontal gyrus compared to the healthy group. In addition, the severity of irritability had significantly negative correlation with the CT of right superior frontal gyrus (partial $r = -.48$) in the correlation analysis; see Table S3 and 3 and Figure 2. In Table S3 and 3, we also reported other regions showing significantly increased CT of the left superior temporal gyrus, right parahippocampal gyrus, and left short insular gyrus in group analysis, as well as regions including the right pre/postcentral gyrus showing significant negative correlation with the severity of irritability. For the correlation result of the entire group, see Supplemental Material Section 2.

3.3.3 | LGI: group analysis and the severity of irritability within the patients with severe irritability

In line with the results of VBM and SBM mentioned above, in the between-group analysis, the severe irritability group exhibited decreased LGI in the superior frontal gyrus and middle frontal gyrus compared to the healthy youths, after controlling age, sex, and IQ; see Table S4. In Table S4, we also reported the other regions showing decreased LGI, including left short insular gyri and left superior temporal gyrus in the severe irritability group compared to the healthy group. The LGI analysis within the severe irritability group showed clusters in the right middle temporal gyrus (partial $r = -.38$) right superior part of the precentral sulcus (partial $r = -.35$), left postcentral sulcus (partial $r = -.26$), and right medial orbital sulcus (partial $r = -.42$) with a significant negative correlation of LGI with the severity of irritability (Figure 3 and Table 4). For the correlation result of the entire group, see Supplemental Material Section 3.

4 | DISCUSSION

In this study, we aimed to determine the structural aberrations in youths with severe irritability, by comprehensive and simultaneous assessment of CT, GMV, and LGI. There are two main findings. First, the decreased CT, GMV, and LGI in the right SFG was commonly found in youths with severe irritability compared to healthy youths. In addition, CT, GMV, and LGI of the right SFG were negatively

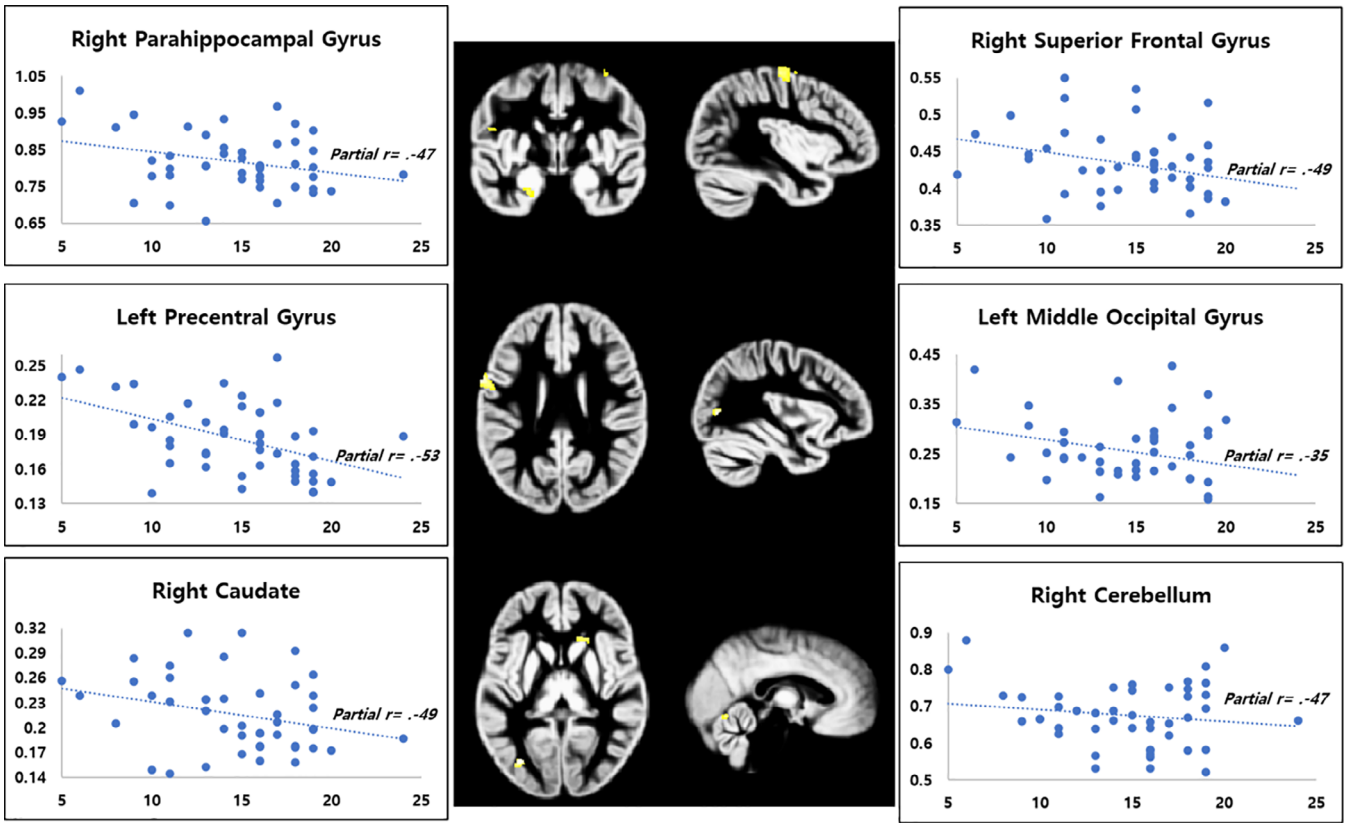

FIGURE 1 VBM correlation analysis ($p < .001$, uncorrected) in the severe irritability group. Brain regions that show a negative correlation with the severeness of irritability (ARI scores). Right superior frontal gyrus (peak MNI coordinate: [39, −17, 65]); right parahippocampal gyrus (peak MNI coordinate: [−23, −5, −30]); left precentral gyrus (peak MNI coordinate: [−65, 6, 24]); left middle occipital gyrus (peak MNI coordinate: [−33, −75, 6]); right caudate (peak MNI coordinate: [20, 26, 9]); right cerebellum (peak MNI coordinate: [−2, −68, −11]). The *x*-axis represents the ARI score, and the *y*-axis shows the relative amount of GMV

correlated with the severity of irritability (i.e., ARI score) in youths with severe irritability. Second, there were other regions than SFG where GMV and LGI were significantly decreased in youths with irritability but without corresponding evidence of CT changes. These regions included the left insula, right parahippocampal gyrus, and left superior temporal gyrus. In summary, the current findings suggest that structural impairment in the SFG (CT, GMV, and LGI) may be associated with severe irritability in youths. Different indices of cortical macrostructure can be helpful to provide additional and complementary information in interpreting the structural changes in this finding.

Previous structural MRI studies have reported that irritability is linked to aberrations in the fronto-striatal-temporal regions (Adleman et al., 2012; Dennis et al., 2019; Gold et al., 2016; Jirsaraie et al., 2019; Pagliaccio et al., 2018). Our finding confirms this by showing reduced fronto-striatal-temporal volumes in the GMV analysis, including the bilateral frontal cortex (BA 6, 8, 9, and 10), bilateral putamen, and left temporal gyrus (BA 20, 21, and 37), in youths with severe irritability compared to healthy youths (Table S2). Recent fMRI studies using response inhibition tasks or emotion labeling tasks showed that higher levels of irritability were related to increased neural activation in the fronto-striatal-temporal regions including the frontal gyrus, parahippocampal gyrus, anterior cingulate, and striatum, suggesting that youths with higher levels of irritability may require more neural resources in these areas to compensate for poor inhibitory control performance (Deveney et al., 2012; Deveney et al., 2013; Singh et al., 2010; Stoddard et al., 2017; Tseng et al., 2019; Wiggins et al., 2016). Previous studies of youths with diagnoses of ADHD or autism spectrum disorder indicated that dysfunctional fronto-striatal-temporal regions may be implicated in impairment in inhibitory control, which might be a contributing factor to irritability as well (Langen et al., 2012; Liuzzi et al., 2020; McAlonan et al., 2009).

Among the fronto-striatal-temporal regions, we recurrently identified the reduction of right SFG in the - CT, GMV, and LGI results (Tables S2, S3, and S4), and the negative relationship between the CT, GMV, and LGI of the SFG and the severity of irritability in youths with severe irritability (Tables 2, 3, and 4). The SFG is located at the superior part of the prefrontal cortex and includes multiple cytoarchitecturally different subregions such as the Brodmann areas (BAs) 4, 6, 8, 9, and 32 (Li et al., 2013; Petrides & Pandya, 2002). The part of SFG shown in this study corresponds to the supplementary motor area (SMA), preSMA, and a part of the premotor cortex (BA 4 and 6). Prior studies reported that this region is connected with the opercular part of the inferior frontal gyrus, precentral gyrus, middle cingulate cortex, and striatum (Ford, McGregor, Case, Crosson, & White, 2010)

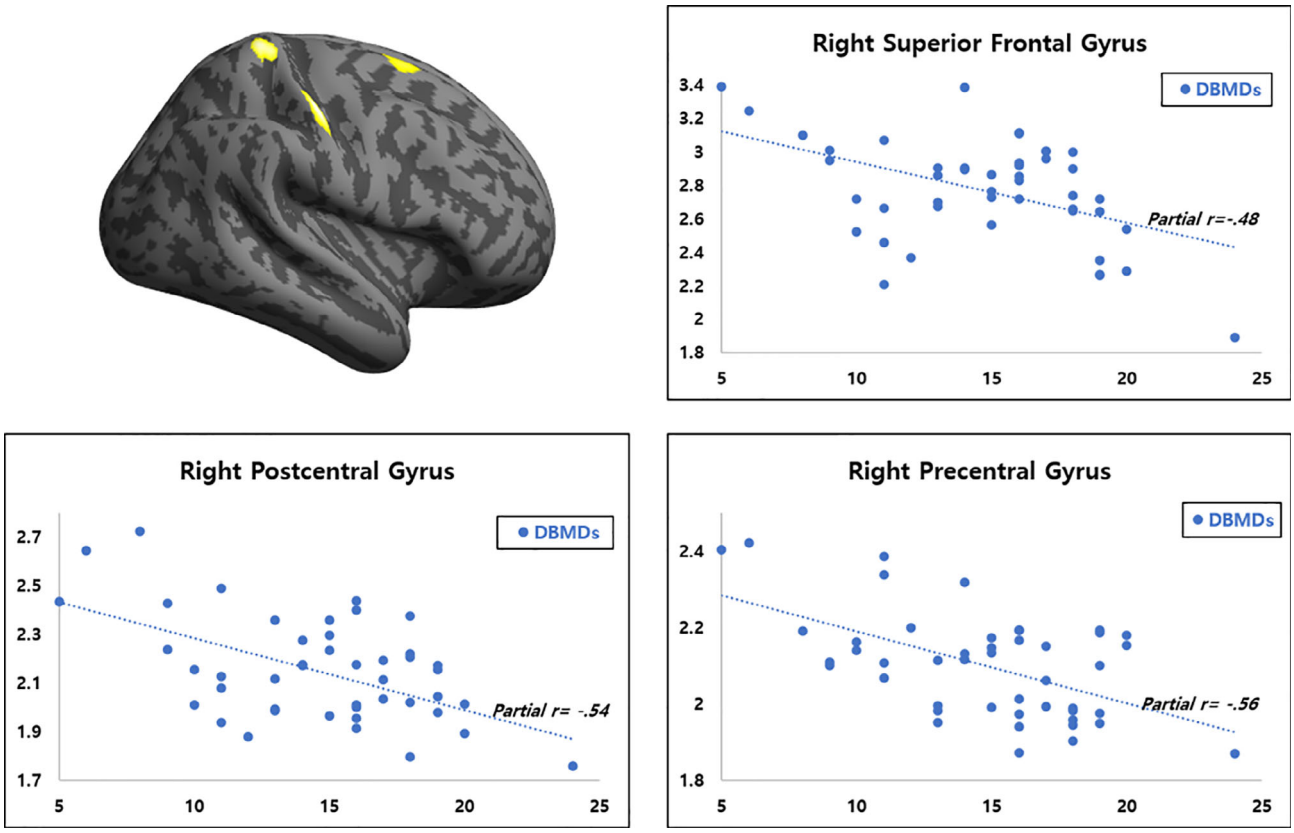

FIGURE 2 SBM correlation analysis in the severe irritability group ($p < .001$, uncorrected at peak level). Clusters that had significant correlation of CT with ARI scale values. The *x*-axis represents the ARI score, and the *y*-axis shows the CT

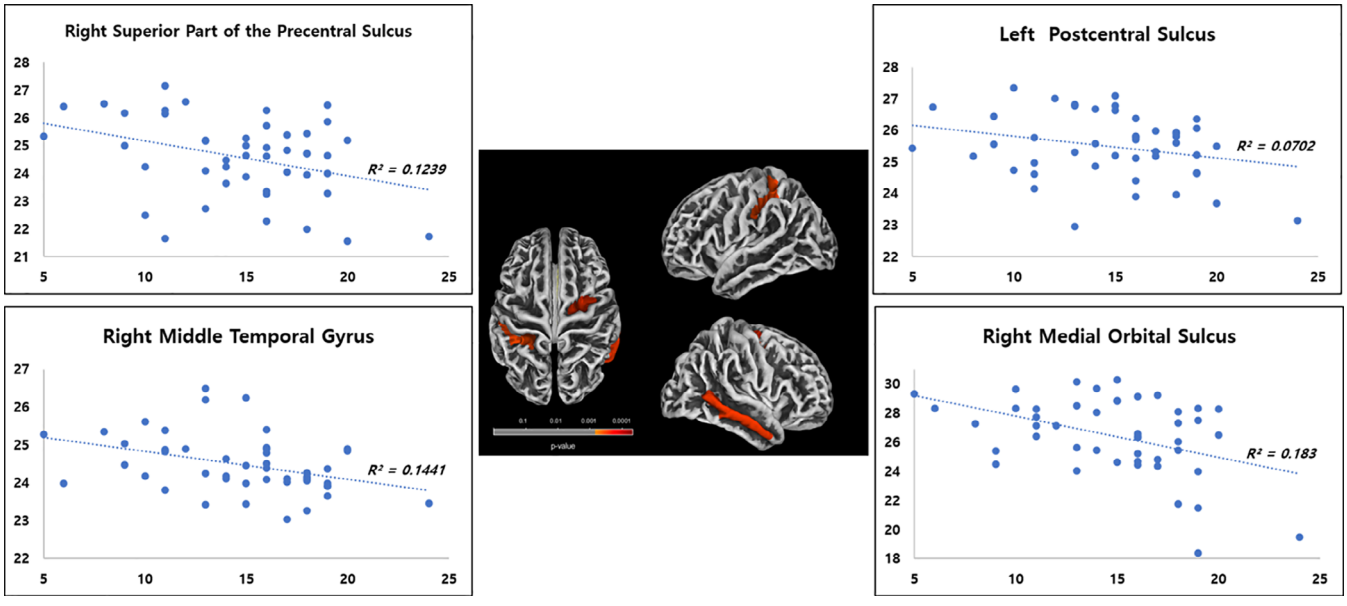

FIGURE 3 Links between LGI and severity of irritability in the severe irritability group. Shown are correlations at $p \leq .001$, uncorrected for multiple comparisons. The *x*-axis represents the ARI score, and the *y*-axis shows the LGI

and serves functions of motor control or top-down cognitive control including conflict monitoring, error detection, response selection, and attention control (Chouinard & Paus, 2010; Li et al., 2013; Martino et al., 2011; Nachev, Kennard, & Husain, 2008). Recently, Fishburn and his colleagues explored the relationship between frontal cortex activation during inhibitory control and the entire set of

TABLE 2 Regions showing significant correlation between GMV and severity of irritability in the severe irritability group

Brain region	Label (BA)	MNI coordinates x	y	z	T_{max}	Number of voxel
Negative correlation						
Right superior frontal gyrus	4, 6	39	−17	65	4.06	245
		38	−5	66	3.55	
Left precentral gyrus	6, 9, 44	−65	6	24	4.48	261
Inferior frontal gyrus		−51	−6	20	3.62	
		−50	−3	11	3.59	
Left parahippocampal gyrus	36	−23	−5	−30	3.84	72
Right caudate		20	26	9	4.14	128
Left middle occipital gyrus	19	−33	−75	6	4.68	78
Left cerebellum	VI	−2	−68	−11	3.97	45

Abbreviations: BA, Brodmann area; MNI, Montreal Neurological Institute.
Note: MNI coordinates of the maximum *t*-scores are shown for each cluster. Results are reported at $p < .001$, uncorrected for the whole-brain analysis.

TABLE 3 Regions showing significant correlation between CT and severity of irritability in the severe irritability group

Brain region	MNI coordinates x	y	z	T_{max}	Number of voxel
Negative correlation					
Right superior frontal gyrus	20	7	67	3.52	52
Right precentral gyrus	45	−14	55	4.35	102
Right postcentral gyrus	18	−40	67	4.12	110

Note: MNI coordinates of the maximum *t*-scores are shown for each cluster. Results are reported at $p < .001$, uncorrected for the whole-brain analysis.

TABLE 4 Regions showing significant correlation between LGI and severity of irritability in the severe irritability group

Overlap of atlas region	Cluster size	*p* (uncorrected)	T_{max}
Negative correlation			
100% right superior part of the precentral sulcus	1,920	<.001	3.52
100% left postcentral sulcus	4,447	<.001	3.40
100% right middle temporal gyrus	3,137	<.001	3.57
100% right medial orbital sulcus	951	<.001	3.65

Note: Results are reported at $p < .001$, uncorrected.

temperamental dimensions including anger/frustration, impulsivity, and low intensity pleasure (Fishburn et al., 2019). They found that anger/frustration among temperament domains was uniquely predictive of the amount of activation positively related to inhibitory control. Taken together, these finding suggest a significant role of the attenuated SFG in the inhibitory control deficit, likely leading to the symptom manifestation of severe irritability (Bonham, Shanley, Waters, & Elvin, 2021).

We observed contradictory results in the left insula, right parahippocampal gyrus, and left superior temporal gyrus among CT, GMV, and LGI. There were reduced GMV and LGI related to severe irritability, but increased CT was shown in these regions in youths with severe irritability compared to healthy youths. This discrepancy between GMV, LGI, and CT may be associated with differences between what the measures of these indices structurally represent. Recent studies demonstrated that the changes of CT and LGI represent changes in laminar structure and folding patterns of the cortical area respectively, while the changes of GMV was mediated by the changes of CT, LGI, CSA and gray/white matter intensity contrast (Hutton et al., 2009; Panizzon et al., 2009; Winkler et al., 2018). Several studies also demonstrated that the indices of cerebral morphology including CT and CSA are not linked genetically (Winkler et al., 2018), influenced by regionally distinct genetic factors (Chen et al., 2011), nor follow different trajectories over the lifespan (Fjell et al., 2015), suggesting CSA and CT are globally and regionally independent, and different biological factors may contribute to the changes in CT and CSA (Chen et al., 2011; Fjell et al., 2015; Rakic, 2007; Winkler et al., 2018). Furthermore, molecular genetics studies suggest that the discrepancy between CT and GMV in these regions may be due to an impaired structural cortical development

(Huttenlocher & Dabholkar, 1997; Huttenlocher, De Courten, Garey, & Van der Loos, 1982; Petanjek et al., 2011; Petanjek, Judaš, Kostović, & Uylings, 2008). The underlying neurobiological mechanisms for developmental changes in CT include both the process leading to early postnatal thickness increase (i.e., proliferation of dendrites, dendritic spines, axonal sprouting, and vascular development) and the process leading to apparent thinning (i.e., synaptic pruning and intracortical myelination) (Huttenlocher et al., 1982; Huttenlocher & Dabholkar, 1997; Petanjek et al., 2008; Petanjek et al., 2011). Specifically, the apparent thinning process could move the boundary detected in MRI between the gray and the white matter outward to the brain surface, thereby causing apparent thinning of the MRI-reconstructed cortex (Fjell et al., 2015). In line with these findings, the increased LGIs of these regions shown in this study may indicate lower degree of cortical maturation and are evidence to explain the increased CT and reduced GMV in youths with severe irritability.

In addition, the different pattern between the SFG (i.e., decreased GMV, LGI, and CT) and the left insula, right parahippocampal gyrus, and left superior temporal gyrus (i.e., decreased GMV, LGI, and increased CT) may be due to the different rates of cortical development by the specific age range of the study population (10–18 years old) in the individual brain regions (Fjell et al., 2015). A study on developmental and lifespan changes in CT showed that there is no similarity for CT by age between the SFG (i.e., motor/pre-motor/SMA area) and the temporal area, and the SFG exhibits more rapid cortical thinning than the temporal lobe under 20 years of age (Fjell et al., 2015).

These findings demonstrate that irritability is associated with structural aberrance in the right SFG, left insula, right parahippocampal gyrus, and left superior temporal gyrus. Different results in individual indices of cortical morphology may be found due to differences in the rate of cortical development in each region.

Several limitations of our study should be noted. First, although there were clear correlations between severity of irritability and volume reduction in various areas (especially in SFG by multiple methods), it should be noted that the sample showed a significant propensity for externalizing diagnoses (82.6% ADHD, 60.9% ODD, 47.8% DMDD, and 21.7% MDD). As such, it is possible that the current results primarily address the structural correlates of increased irritability in adolescents with externalizing conditions rather than cross-diagnostically more generally. It will be important in future work to confirm that the current results are also relevant to irritability in adolescents with internalizing conditions.

Second, although there were clear correlations between severity of irritability and volume reduction in various areas (especially in SFG), it is possible that categorical diagnosis (especially ADHD given the high percentage of participants who had this diagnosis [82.61%]) may be a critical factor in our current findings. However, at the same time, it should be noted that generally not all ADHD patients show severe levels of irritability (39.8% irritable type in ADHD) (Karalunas et al., 2014). Thus, our results may point toward the impact of severity of irritability or at least combined effect of categorical diagnosis and severe irritability rather than any categorical diagnosis alone. Future research is warranted in this regard.

Third, the sample size of youths with severe irritability ($n = 46$) was relatively small for correlation analysis. However, these results have the strength of acquiring data from youths with psychiatric diagnoses confirmed by a structured interview (The Kiddie-Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version, K-SADS-PL) (Kaufman, Birmaher, Brent, Ryan, & Rao, 2000). Also, we presented the additional correlation results obtained from a larger number of participants ($N = 108$) including healthy youths and found a significantly different correlation pattern between groups (see Tables S6–S8 and Figures S1–S3).

Lastly, this was a cross-sectional study and we could not provide any longitudinal observation of the structural abnormalities related to severe level of irritability. Although age was not significantly different and was used as a covariate in all of the analyses, the structural difference observed might reflect normal variation during brain development. However, previous longitudinal MRI work has indicated that GMV in the frontal lobe shows decreased volume during adolescence, after a peak occurring at around 12 (Bansal, Gerber, & Peterson, 2008; Giedd et al., 1999; Lenroot & Giedd, 2006; Semple, Blomgren, Gimlin, Ferriero, & Noble-Haeusslein, 2013). As such, the slightly older healthy control group might be expected to show smaller GMV as a consequence of normal development. This would imply that the current results underplay the GMV irritability findings. Future longitudinal studies are warranted, to investigate potential delay in cortical development/maturation related to irritability in youths (Fjell et al., 2015).

Despite these limitations, this is the first study to investigate differences in CT, GMV, and LGI comprehensively and simultaneously in youths with severe irritability. We provide new evidence that youths with severe irritability demonstrate associated with structural alteration within the right SFG, left insula, right parahippocampal gyrus, and left superior temporal gyrus. Specifically, SFG showed reduced GMV, CT, and LGI, which were associated the level of irritability manifested by the youths. Our findings suggest that structural deficits in regions necessary for inhibitory control, such as the superior frontal gyrus, may be critical for the neurobiology of irritability. Also, the different results of individual indices of cortical morphology in the left insula, right parahippocampal gyrus, and left superior temporal gyrus may be related to differences in the rate of cortical development in each region, suggesting that different indices of cortical morphology provide additional and complementary information and that future studies could benefit from studying several cortical properties simultaneously.

CONFLICT OF INTEREST

None of the authors have conflict of interest to disclose.

ETHICS APPROVAL

The study was reviewed and approved by the institutional review boards of University of Nebraska Medical Center and Boys Town National Research Hospital (protocol number: 321-16-FB).

PATIENT CONSENT

Patient and his/her legal guardian were consented by the consent form approved by the UNMC IRB. The participants and their guardians were given ample time to review and consider study participation, and were encouraged to address any concern or questions regarding study participation. The consent procedure was conducted in private and safe place with trained research personnel.

PERMISSION TO REPRODUCE MATERIAL FROM OTHER SOURCES

There is no material from other sources than material generated by and from the authors and participating institutions.

CLINICAL TRIAL REGISTRATION

The study was registered at clinicaltrials.gov (trial number: NCT02824627).

DATA AVAILABILITY STATEMENT

Raw data were generated at University of Nebraska Medical Center/Boys Town National Research Hospital. Derived data supporting the findings of the study are available from the corresponding author (Soonjo Hwang, M.D.) on request.

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REFERENCES

Adleman, N. E., Fromm, S. J., Razdan, V., Kayser, R., Dickstein, D. P., Brotman, M. A., … Leibenluft, E. (2012). Cross-sectional and longitudinal abnormalities in brain structure in children with severe mood dysregulation or bipolar disorder. *Journal of Child Psychology and Psychiatry*, *53*(11), 1149–1156.

American Psychiatric Association. (2013). *Diagnostic and statistical manual 5*. Washington, DC: American Psychiatric Association.

Ashburner, J. (2007). A fast diffeomorphic image registration algorithm. *NeuroImage*, *38*(1), 95–113.

Ashburner, J., & Friston, K. J. (2000). Voxel-based morphometry—The methods. *NeuroImage*, *11*(6), 805–821.

Ashburner, J., & Friston, K. J. (2005). Unified segmentation. *NeuroImage*, *26*(3), 839–851.

Avenevoli, S., Blader, J. C., & Leibenluft, E. (2015). Irritability in youth: An update. *Journal of the American Academy of Child and Adolescent Psychiatry*, *54*(11), 881–883.

Bansal, R., Gerber, A. J., & Peterson, B. S. (2008). Brain morphometry using anatomical magnetic resonance imaging. *Journal of the American Academy of Child and Adolescent Psychiatry*, *47*(6), 619.

Beauchaine, T. P., & Tackett, J. L. (2020). Irritability as a transdiagnostic vulnerability trait: Current issues and future directions. *Behavior Therapy*, *51*(2), 350–364.

Bonham, M. D., Shanley, D. C., Waters, A. M., & Elvin, O. M. (2021). Inhibitory control deficits in children with oppositional defiant disorder and conduct disorder compared to attention deficit hyperactivity disorder: A systematic review and meta-analysis. *Journal of Abnormal Child Psychology*, *49*, 39–62.

Chen, C.-H., Panizzon, M. S., Eyler, L. T., Jernigan, T. L., Thompson, W., Fennema-Notestine, C., … Hamza, S. (2011). Genetic influences on cortical regionalization in the human brain. *Neuron*, *72*(4), 537–544.

Chouinard, P. A., & Paus, T. (2010). What have we learned from "perturbing" the human cortical motor system with transcranial magnetic stimulation? *Frontiers in Human Neuroscience*, *4*, 173.

Crum, K. I., Hwang, S., Blair, K. S., Aloi, J. M., Meffert, H., White, S. F., … Blair, R. J. R. (2020). Interaction of irritability and anxiety on emotional responding and emotion regulation: A functional MRI study. *Psychological Medicine*, 1–11. https://doi.org/10.1017/s0033291720001397

Dahnke, R., Yotter, R. A., & Gaser, C. (2013). Cortical thickness and central surface estimation. *NeuroImage*, *65*, 336–348.

Dale, A. M., Fischl, B., & Sereno, M. I. (1999). Cortical surface-based analysis: I. Segmentation and surface reconstruction. *NeuroImage*, *9*(2), 179–194.

Dennis, E. L., Humphreys, K. L., King, L. S., Thompson, P. M., & Gotlib, I. H. (2019). Irritability and brain volume in adolescents: Cross-sectional and longitudinal associations. *Social Cognitive and Affective Neuroscience*, *14*(7), 687–698.

Destrieux, C., Fischl, B., Dale, A., & Halgren, E. (2010). Automatic parcellation of human cortical gyri and sulci using standard anatomical nomenclature. *NeuroImage*, *53*(1), 1–15.

Deveney, C. M., Connolly, M. E., Haring, C. T., Bones, B. L., Reynolds, R. C., Kim, P., … Leibenluft, E. (2013). Neural mechanisms of frustration in chronically irritable children. *American Journal of Psychiatry*, *170*(10), 1186–1194.

Deveney, C. M., Connolly, M. E., Jenkins, S. E., Kim, P., Fromm, S. J., Pine, D. S., & Leibenluft, E. (2012). Neural recruitment during failed motor inhibition differentiates youths with bipolar disorder and severe mood dysregulation. *Biological Psychology*, *89*(1), 148–155.

Fischl, B., & Dale, A. M. (2000). Measuring the thickness of the human cerebral cortex from magnetic resonance images. *Proceedings of the National Academy of Sciences*, *97*(20), 11050–11055.

Fishburn, F. A., Hlutkowsky, C. O., Bemis, L. M., Huppert, T. J., Wakschlag, L. S., & Perlman, S. B. (2019). Irritability uniquely predicts prefrontal cortex activation during preschool inhibitory control among all temperament domains: A LASSO approach. *NeuroImage*, *184*, 68–77.

Fjell, A. M., Grydeland, H., Krogsrud, S. K., Amlien, I., Rohani, D. A., Ferschmann, L., … Due-Tønnessen, P. (2015). Development and aging of cortical thickness correspond to genetic organization patterns. *Proceedings of the National Academy of Sciences*, *112*(50), 15462–15467.

Ford, A., McGregor, K. M., Case, K., Crosson, B., & White, K. D. (2010). Structural connectivity of Broca's area and medial frontal cortex. *NeuroImage*, *52*(4), 1230–1237.

Giedd, J. N., Blumenthal, J., Jeffries, N. O., Castellanos, F. X., Liu, H., Zijdenbos, A., … Rapoport, J. L. (1999). Brain development during childhood and adolescence: A longitudinal MRI study. *Nature Neuroscience*, *2*(10), 861–863.

Gold, A. L., Brotman, M. A., Adleman, N. E., Lever, S. N., Steuber, E. R., Fromm, S. J., … Leibenluft, E. (2016). Comparing brain morphometry across multiple childhood psychiatric disorders. *Journal of the American Academy of Child & Adolescent Psychiatry*, *55*(12), 1027–1037 e1023.

Greve, D. N., & Fischl, B. (2018). False positive rates in surface-based anatomical analysis. *NeuroImage*, *171*, 6–14.

Huttenlocher, P. R., & Dabholkar, A. S. (1997). Regional differences in synaptogenesis in human cerebral cortex. *Journal of Comparative Neurology*, *387*(2), 167–178.

Huttenlocher, P. R., De Courten, C., Garey, L. J., & Van der Loos, H. (1982). Synaptic development in human cerebral cortex. *International Journal of Neurology*, *16*, 144.

Hutton, C., Draganski, B., Ashburner, J., & Weiskopf, N. (2009). A comparison between voxel-based cortical thickness and voxel-based morphometry in normal aging. *NeuroImage*, *48*(2), 371–380.

Jirsaraie, R. J., Kaczkurkin, A. N., Rush, S., Piiwia, K., Adebimpe, A., Bassett, D. S., … Ciric, R. (2019). Accelerated cortical thinning within structural brain networks is associated with irritability in youth. *Neuropsychopharmacology*, *44*(13), 2254–2262.

Karalunas, S. L., Fair, D., Musser, E. D., Aykes, K., Iyer, S. P., & Nigg, J. T. (2014). Subtyping attention-deficit/hyperactivity disorder using temperament dimensions: Toward biologically based nosologic criteria. *JAMA Psychiatry*, *71*(9), 1015–1024.

Kaufman, J., Birmaher, B., Brent, D., Rao, U., Flynn, C., Moreci, P., … Ryan, N. (1997). Schedule for affective disorders and schizophrenia for school-age children-present and lifetime version (K-SADS-PL): Initial reliability and validity data. *Journal of the American Academy of Child & Adolescent Psychiatry*, *36*(7), 980–988.

Kaufman, J., Birmaher, B., Brent, D. A., Ryan, N. D., & Rao, U. (2000). K-SADS-PL. *Journal of the American Academy of Child & Adolescent Psychiatry*, *39*(10), 1208.

Kelly, P. A., Viding, E., Wallace, G. L., Schaer, M., De Brito, S. A., Robustelli, B., & McCrory, E. J. (2013). Cortical thickness, surface area, and gyrification abnormalities in children exposed to maltreatment: Neural markers of vulnerability? *Biological Psychiatry*, *74*(11), 845–852.

Langen, M., Leemans, A., Johnston, P., Ecker, C., Daly, E., Murphy, C. M., … Consortium, A. (2012). Fronto-striatal circuitry and inhibitory control in autism: Findings from diffusion tensor imaging tractography. *Cortex*, *48*(2), 183–193.

Leblanc, É., Dégeilh, F., Daneault, V., Beauchamp, M. H., & Bernier, A. (2017). Attachment security in infancy: A preliminary study of prospective links to brain morphometry in late childhood. *Frontiers in Psychology*, *8*, 2141.

Lee, D., Kwak, S., & Chey, J. (2019). Parallel changes in cognitive function and gray matter volume after multicomponent training of cognitive control (MTCC) in adolescents. *Frontiers in Human Neuroscience*, *13*, 246.

Leibenluft, E. (2017). Irritability in children: What we know and what we need to learn. *World Psychiatry*, *16*(1), 100.

Leibenluft, E., Blair, R. J. R., Charney, D. S., & Pine, D. S. (2003). Irritability in pediatric mania and other childhood psychopathology. *Annals of the New York Academy of Sciences*, *1008*(1), 201–218.

Lenroot, R. K., & Giedd, J. N. (2006). Brain development in children and adolescents: Insights from anatomical magnetic resonance imaging. *Neuroscience & Biobehavioral Reviews*, *30*(6), 718–729.

Li, W., Qin, W., Liu, H., Fan, L., Wang, J., Jiang, T., & Yu, C. (2013). Subregions of the human superior frontal gyrus and their connections. *NeuroImage*, *78*, 46–58.

Liuzzi, M. T., Kryza-Lacombe, M., Christian, I. R., Palumbo, D., Amir, N., & Wiggins, J. L. (2020). Neural and behavioral correlates of inhibitory control in youths with varying levels of irritability. *Journal of Affective Disorders*, *273*, 567–575. https://doi.org/10.1016/j. jad.2020.04.049.

Luders, E., Thompson, P. M., Narr, K., Toga, A. W., Jancke, L., & Gaser, C. (2006). A curvature-based approach to estimate local gyrification on the cortical surface. *NeuroImage*, *29*(4), 1224–1230.

Martino, J., Gabarrós, A., Deus, J., Juncadella, M., Acebes, J., Torres, A., & Pujol, J. (2011). Intrasurgical mapping of complex motor function in the superior frontal gyrus. *Neuroscience*, *179*, 131–142.

McAlonan, G. M., Cheung, V., Chua, S. E., Oosterlaan, J., Hung, S.-F., Tang, C.-P., … Cheung, C. (2009). Age-related grey matter volume correlates of response inhibition and shifting in attention-deficit hyperactivity disorder. *The British Journal of Psychiatry*, *194*(2), 123–129.

Mulraney, M. A., Melvin, G. A., & Tonge, B. J. (2014). Psychometric properties of the affective reactivity index in Australian adults and adolescents. *Psychological Assessment*, *26*(1), 148.

Nachev, P., Kennard, C., & Husain, M. (2008). Functional role of the supplementary and pre-supplementary motor areas. *Nature Reviews Neuroscience*, *9*(11), 856–869.

Pagliaccio, D., Pine, D. S., Barch, D. M., Luby, J. L., & Leibenluft, E. (2018). Irritability trajectories, cortical thickness, and clinical outcomes in a sample enriched for preschool depression. *Journal of the American Academy of Child & Adolescent Psychiatry*, *57*(5), 336–342 e336.

Panizzon, M. S., Fennema-Notestine, C., Eyler, L. T., Jernigan, T. L., Prom-Wormley, E., Neale, M., … Franz, C. E. (2009). Distinct genetic influences on cortical surface area and cortical thickness. *Cerebral Cortex*, *19*(11), 2728–2735.

Petanjek, Z., Judaš, M., Kostović, I., & Uylings, H. B. (2008). Lifespan alterations of basal dendritic trees of pyramidal neurons in the human prefrontal cortex: A layer-specific pattern. *Cerebral Cortex*, *18*(4), 915–929.

Petanjek, Z., Judaš, M., Šimić, G., Rašin, M. R., Uylings, H. B., Rakic, P., & Kostović, I. (2011). Extraordinary neoteny of synaptic spines in the human prefrontal cortex. *Proceedings of the National Academy of Sciences*, *108*(32), 13281–13286.

Petrides, M., & Pandya, D. (2002). Comparative cytoarchitectonic analysis of the human and the macaque ventrolateral prefrontal cortex and corticocortical connection patterns in the monkey. *European Journal of Neuroscience*, *16*(2), 291–310.

Rakic, P. (1988). Specification of cerebral cortical areas. *Science*, *241* (4862), 170–176.

Rakic, P. (2007). The radial edifice of cortical architecture: From neuronal silhouettes to genetic engineering. *Brain Research Reviews*, *55*(2), 204–219.

Righart, R., Schmidt, P., Dahnke, R., Biberacher, V., Beer, A., Buck, D., … Gaser, C. (2017). Volume versus surface-based cortical thickness measurements: A comparative study with healthy controls and multiple sclerosis patients. *PLoS One*, *12*(7), e0179590.

Schaer, M., Cuadra, M. B., Tamarit, L., Lazeyras, F., Eliez, S., & Thiran, J.-P. (2008). A surface-based approach to quantify local cortical gyrification. *IEEE Transactions on Medical Imaging*, *27*(2), 161–170.

Seiger, R., Ganger, S., Kranz, G. S., Hahn, A., & Lanzenberger, R. (2018). Cortical thickness estimations of freesurfer and the CAT12 toolbox in patients with Alzheimer's disease and healthy controls. *Journal of Neuroimaging*, *28*(5), 515–523.

Semple, B. D., Blomgren, K., Gimlin, K., Ferriero, D. M., & Noble-Haeusslein, L. J. (2013). Brain development in rodents and humans: Identifying benchmarks of maturation and vulnerability to injury across species. *Progress in Neurobiology*, *106*, 1–16.

Singh, M. K., Chang, K. D., Mazaika, P., Garrett, A., Adleman, N., Kelley, R., … Reiss, A. (2010). Neural correlates of response inhibition in pediatric bipolar disorder. *Journal of Child and Adolescent Psychopharmacology*, *20*(1), 15–24.

Stoddard, J., Tseng, W.-L., Kim, P., Chen, G., Yi, J., Donahue, L., … Leibenluft, E. (2017). Association of irritability and anxiety with the neural mechanisms of implicit face emotion processing in youths with psychopathology. *JAMA Psychiatry*, *74*(1), 95–103.

Stringaris, A., Goodman, R., Ferdinando, S., Razdan, V., Muhrer, E., Leibenluft, E., & Brotman, M. A. (2012). The affective reactivity index: A concise irritability scale for clinical and research settings. *Journal of Child Psychology and Psychiatry*, *53*(11), 1109–1117.

Tseng, W.-L., Deveney, C. M., Stoddard, J., Kircanski, K., Frackman, A. E., Yi, J. Y., … Donahue, L. (2019). Brain mechanisms of attention orienting following frustration: Associations with irritability and age in youths. *American Journal of Psychiatry*, *176*(1), 67–76.

Wechsler, D. (2011). *Wechsler abbreviated scale of intelligence–second edition*. San Antonio, TX: NCS Pearson.

Wiggins, J. L., Brotman, M. A., Adleman, N. E., Kim, P., Oakes, A. H., Reynolds, R. C., … Leibenluft, E. (2016). Neural correlates of irritability in disruptive mood dysregulation and bipolar disorders. *American Journal of Psychiatry*, *173*(7), 722–730.

Winkler, A. M., Greve, D. N., Bjuland, K. J., Nichols, T. E., Sabuncu, M. R., Håberg, A. K., … Rimol, L. M. (2018). Joint analysis of cortical area and thickness as a replacement for the analysis of the volume of the cerebral cortex. *Cerebral Cortex*, *28*(2), 738–749.

Winkler, A. M., Kochunov, P., Blangero, J., Almasy, L., Zilles, K., Fox, P. T., … Glahn, D. C. (2010). Cortical thickness or grey matter volume? The importance of selecting the phenotype for imaging genetics studies. *NeuroImage*, *53*(3), 1135–1146.

Yotter, R. A., Nenadic, I., Ziegler, G., Thompson, P. M., & Gaser, C. (2011). Local cortical surface complexity maps from spherical harmonic reconstructions. *NeuroImage*, *56*(3), 961–973.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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