Irritability and brain volume in adolescents: cross-sectional and longitudinal associations

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Abstract

Irritability is garnering increasing attention in psychiatric research as a transdiagnostic marker of both internalizing and externalizing disorders. These disorders often emerge during adolescence, highlighting the need to examine changes in the brain and in psychological functioning during this developmental period. Adolescents were recruited for a longitudinal study examining the effects of early life stress on the development of psychopathology. The 151 adolescents (73 M/78 F, average age = 11.5 years, standard deviation = 1.1) were scanned with a T1-weighted MRI sequence and parents completed reports of adolescent irritability using the Affective Reactivity Index. Of these 151 adolescents, 94 (46 M/48 F) returned for a second session (average interval = 1.9 years, SD = 0.4). We used tensor-based morphometry to examine cross-sectional and longitudinal associations between irritability and regional brain volume. Irritability was associated with brain volume across a number of regions. More irritable individuals had larger hippocampi, insula, medial orbitofrontal cortex and cingulum/cingulate cortex and smaller putamen and internal capsule. Across the brain, more irritable individuals also had larger volume and less volume contraction in a number of areas that typically decrease in volume over the developmental period studied here, suggesting delayed maturation. These structural changes may increase adolescents' vulnerability for internalizing and externalizing disorders.

Key words: irritability; brain structure; tensor-based morphometry; development

Introduction

There is growing interest in the construct of irritability (Vidal-Ribas *et al.,* 2016; Stringaris *et al.,* 2018). Irritability has been conceptualized as 'proneness to anger,' although it can also refer to difficulty disengaging from an angry state (Stringaris *et al.,* 2012). Prospective studies indicate that irritability increases

individuals' risk for a number of negative outcomes, including major depressive disorder (Stringaris *et al.,* 2009), suicidality (Pickles *et al.,* 2010) and general functional impairment (Dougherty *et al.,* 2015). Irritability has recently been formulated to be transdiagnostic; indeed, irritability has been associated with both internalizing and externalizing disorders in cross-sectional and longitudinal studies (Leibenluft *et al.,* 2006;

Stoddard *et al.,* 2014; Humphreys *et al.,* 2018). Given that these disorders increase in prevalence during adolescence (Lee *et al.,* 2014), examining the neural correlates of irritability during the transition from earlier to later adolescence may help to elucidate the biological mechanisms involved in the development of psychopathology and other negative long-term outcomes.

Several studies have now examined the neural basis of irritability; however, there are specific limitations of these studies that justify additional research in this area. Few studies have examined the association between irritability and alterations in brain structure. Most of these structural studies have used a group-based approach to operationalize irritability. Gold et al. (2016) used voxel-based morphometry (VBM) to examine brain morphometry in children with and without diagnosed psychiatric disorders. In contrast to healthy comparison children, children with disruptive mood dysregulation disorder (DMDD) had lower overall gray matter volume in right dorsolateral prefrontal cortex (dlPFC)/superior frontal gyrus; however, across all groups, irritability was not associated significantly with variation in brain morphometry. Using VBM in a sample of 78, 13- to 14-year-old adolescents with severe mood dysregulation (SMD) and 68 age-matched healthy comparison adolescents (Adleman *et al.,* 2012) found in cross-sectional analyses that youth with SMD had significantly lower gray matter density in bilateral pre-supplementary motor area, right insula and dlPFC than did healthy controls. Longitudinal analyses from these same participants 2 years later yielded no significant group differences or interactions of group and time. In another longitudinal sample, enriched for the presence of early depressive symptoms, in which irritability was operationalized dimensionally, Pagliaccio et al. (2018) found thicker cortex in the left superior frontal gyrus, left superior temporal gyrus and right inferior parietal lobule in a subset of children who exhibited consistently elevated levels of irritability.

There have been a few functional MRI (fMRI) studies focused on irritability, with some focused on individuals with SMD, which is characterized by persistent, elevated and functionally impairing levels of irritability (Leibenluft, 2011) or DMDD (American Psychiatic Association, 2013). fMRI studies of individuals with DMDD or SMD have reported increased amygdala reactivity to both positive and negative emotional faces (Wiggins *et al.,* 2016) and deactivation in the amygdala, striatum, parietal cortex and posterior cingulate in response to frustration (Deveney *et al.,* 2013). The application of findings from these studies to individuals who do not meet criteria for disorder but nonetheless evidence elevated irritability may be limited. In some studies, however, irritability has been operationalized as a dimensional construct, generally assessed using metrics that map onto the Research Domain Criteria construct of 'frustrative non-reward' (Insel *et al.,* 2010). In studies using samples recruited based on broader risk metrics, including adolescents with DMDD, anxiety disorders or attention-deficit/hyperactivity disorder (ADHD), higher scores on the Affective Reactivity Index (ARI), reflecting higher levels of irritability, were associated with decreased connectivity between the amygdala and prefrontal cortex (Stoddard *et al.,* 2017), increased fronto-striatal activity in response to frustration (Tseng *et al.,* 2018) and increased activity in the insula, caudate, prefrontal cortex and inferior parietal lobule while orienting away from threat (Kircanski *et al.,* 2018). Examining a sample of young children with clinically significant levels of irritability and at least one psychiatric diagnosis, Perlman et al. (2015) found that dimensionally assessed irritability was associated with decreased activation in the anterior cingulate cortex (ACC) and the striatum during

the experience of loss on a reward task. Further, group-based analyses in that study indicated that, relative to healthy comparison children, clinical participants had greater activation in the ACC and middle frontal gyrus (MFG) during a reward task, but reduced activation in these structures during a frustration task. Finally, the clinical participants exhibited less activation of the posterior cingulate than did the healthy control participants during reward, but more activation during frustration.

While it has been useful to use a group-based approach to examine irritability, it is likely that irritability is not a taxon. As employed by some prior studies, it is important that irritability be studied dimensionally, as data indicate that related constructs are best conceptualized dimensionally (Ruscio and Ruscio, 2000). Moreover, including participants across a range of functioning, as opposed to studying irritability in clinical samples of children, increases generalization to the broader population. Finally, most of the studies reviewed above included participants in a large age range (8–20 years old). Given that psychopathology often emerges during adolescence (Lee *et al.,* 2014), it is critical that we assess individuals in this developmental stage—early adolescence prior to the onset of psychopathology. No study to date, however, has investigated associations between brain structure and irritability dimensionally in adolescents who were not selected on the basis of exhibiting symptoms of psychopathology. The present study examined the cross-sectional and longitudinal associations between irritability and brain structure in a cohort of typically developing adolescents. We assessed 151 participants in early adolescence, 94 of whom returned for a longitudinal follow-up session in later adolescence. To measure brain structure at each time point, we used tensor-based morphometry (TBM), which allowed us to conduct a whole-brain search of structural correlates of irritability that was not constrained by *a priori* hypotheses. Although VBM has been used in previous studies of irritability (Adleman *et al.,* 2012; Gold *et al.,* 2016) and is also a whole-brain approach, TBM has several advantages over VBM (Thompson *et al.,* 2000). For example, TBM does not involve tissue segmentation or spatial smoothing steps, which can introduce error and limit resolution for small effects. Further, VBM depends on tissue density measurements to calculate differences, which require high-quality registration, and inaccuracies can erroneously be identified as differences in volume (Bookstein, 2001). FreeSurfer has a well-validated set of tools for cortical analyses (Fischl, 2012), but these do not allow for whole brain, voxel-wise analysis of volume. Further, in a direct comparison of cortical thickness estimates from FreeSurfer and Advanced Normalization Tools (ANTs—the toolbox used in our TBM workflow), ANTs had stronger neurobiological validity in predicting age and sex (Tustison *et al.,* 2014). We did not limit our analysis to specific regions; indeed, previous studies have not identified structural alterations in a cohesive set of brain regions related to irritability. Based on the fMRI research cited above, however, we hypothesized that irritability would be associated with altered volume in fronto-striatal structures, the amygdala and the insular cortex.

Materials and methods

Participants

Participants in the larger study were 214 children (93 boys, 121 girls) ages 9.1 to 13.9 years (mean age: 11.4 years, SD = 1.0) who were recruited to take part in a longitudinal study of psychopathology across the pubertal transition [see (Humphreys *et al.,* 2016) for more information on the sample]. Participants
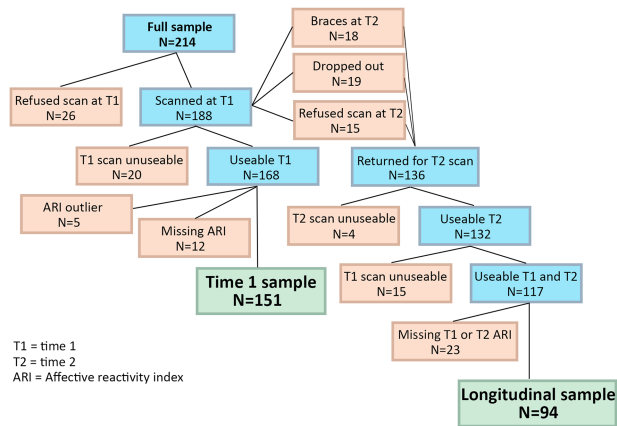
Fig. 1. Flowchart of sample. Of the full study sample of 214 adolescents, 151 had ARI scores and brain scans of adequate quality for cross-sectional analyses and 94 had complete data for longitudinal analyses.

were selected from the San Francisco Bay community using a combination of flyers and local media; they were recruited on the basis of having experienced a range of early life adversity and were selected for participation if they were in the early stages of puberty (Tanner staging <4). The study was approved by the Stanford University Institutional Review Board; participants and their parents gave assent and informed consent, respectively. Participants were screened for initial inclusion/exclusion criteria through a telephone interview; potentially eligible individuals were then invited to the laboratory for in-person interviews and assessments. Inclusion criteria were that children be between the ages of 9 and 13 years and be proficient in English. Exclusion criteria were factors that would preclude an MRI scan (e.g. metal implants, braces), a history of major neurological or medical illness and severe learning disabilities that would make it difficult for participants to comprehend the study procedures. Females who reported having started menses were excluded, and boys were matched to girls with respect to Tanner stage. Because females enter puberty at an earlier age than males, this meant that the females were significantly younger than the males at both time points (female average age at first study time point = 11.2 years; male average age = 11.9 years, $P = 4.4 \times 10^{-5}$). Participants were compensated for their time.

A flow chart detailing the final sample size is presented in Figure 1. As detailed in the chart, of the 214 participants who started in the study, 151 (73 boys, 78 girls) had useable MRI and ARI data cross-sectionally at T1. Of these participants, 136 have returned for a Time 2 (T2) scan ~2 years after the T1 session (mean interval: 1.9 years, SD = 0.39) for a second visit at which the same assessments were conducted; 94 of these participants had useable longitudinal MRI and ARI data. Scan quality was visually checked during the scan session so that poor-quality scans could be repeated. Nevertheless, some participants still did not provide usable data on repeated scans due to excessive motion and, therefore, were excluded from analyses. The participants who opted out of the scan did not differ significantly from participants included in this report in levels of irritability. Demographic information for participants included in the present analyses is presented in Table 1. There were no significant differences in T1 irritability between participants who have and who have not yet returned for the T2 assessment (P = 0.48, Figure 2). Participants who were not included in the longitudinal analyses also did not differ from participants who

were included in these analyses in age, sex distribution, ethnic distribution, Tanner stage or intracranial volume (all $P > 0.10$). Correlations among measures are presented in Supplementary Table S1.

Procedure

To assess irritability, the participants' parents completed the ARI (Stringaris et al., 2012), a seven-item questionnaire that assesses their child's irritability during the preceding 6 months (six symptom items and one function impairment item). Responses were scored on a three-point scale, from 0 (*not true*) to 2 (*certainly true*), and the 6 items that comprise the total score were summed. To limit the impact of extreme values, we excluded participants with ARI scores more than three SD above the sample mean at either T1 or T2. This excluded five participants. Prior work has indicated that the ARI is a reliable and valid measure of irritability in youth (Stringaris et al., 2012), although it does suffer from floor effects (Stoddard et al., 2014). In this sample, the internal consistency of the ARI was high at both T1 ($\alpha = 0.86$) and T2 ($\alpha = 0.89$). Informant agreement for child psychopathology is known to be low (De Los Reyes and Kazdin, 2004); because no specific informant is considered the gold standard reporter for irritability, we used parent report rather than child report, given that more parents than children provided ARI data (N with parent ARI = 151; N with child ARI = 143). The correlation between parent and child report for those with both reports was $r = 0.37$ ($P < 0.001$).

Scan

MRI scans were acquired at the Center for Cognitive and Neurobiological Imaging at Stanford University using a 3 T Discovery MR750 (GE Medical Systems, Milwaukee, WI, USA) equipped with a 32-channel head coil (Nova Medical, Wilmington, MA, USA). Whole-brain T1-weighted images (T1w) were collected using the following spoiled gradient echo pulse sequence: 186 sagittal slices; TR (repetition time)/TE (echo time)/TI (inversion time) = 6.24/2.34/450 ms; flip angle = 12°; voxel size = 0.9 mm × 0.9 mm × 0.9 mm; scan duration = 5:15 min.

Tensor-based morphometry

At both time points, each participant's T1-weighted anatomical data were N3-corrected using c3d (http://www.itksnap.org) to correct for intensity inhomogeneities. Volumes were automatically skull-stripped using FreeSurfer and brain masks were manually edited to remove extraneous skull or meninges by trained neuroanatomical experts (LS and AC, see Acknowledgements). We used *flirt* (http://fsl.fmrib.ox.ac.uk) to linearly register each participant to a study-specific template. We used a study-specific registration template to obtain the strongest possible registration results (Hua et al., 2013). We chose a female aged 11 years 5 months (the average for the sample subset included) with a visually normal T1-weighted scan to initialize the linear registration. This exemplar participant was registered to the ICBM template using *flirt*, using 7 degrees of freedom registration with trilinear interpolation and using mutual information as the similarity function for alignment. Following this, each participant's masked, N3-corrected T1-weighted image was registered to the participant-template using iterative 6-, 7- and 9-DOF (degrees of freedom) registration. We concatenated transformation files so that only one resampling step was run. This protocol was modified for this data set from the original protocol

Table 1. Demographics of sample

	Cross-sectional sample			Longitudinal sample		
	N	151			**N**	94
	M/F	73/78			**M/F**	46/48
T1 Age	*Average*	11.5		T1 Age	*Average*	11.5
	SD	1.1			*SD*	1.0
	Range	9.2–14.0			*Range*	9.4–13.9
T1 Tanner stage	*Average*	2.0		T1 Tanner stage	*Average*	2.0
	SD	0.7			*SD*	0.8
	Range	1–4			*Range*	1–4
Race/ethnicity	*Caucasian*	70		Race/ethnicity	*Caucasian*	49
	African American	12			*African American*	7
	Hispanic	9			*Hispanic*	6
	Asian/Pacific Islander	19			*Asian/Pacific Islander*	14
	Multi-racial	32			*Multi-racial*	13
	Other or NA	9			*Other or NA*	4
Household income	*Less than $5000*	1		Household income	*Less than $5000*	1
	$5001–$10 000	2			*$5001–$10 000*	2
	$10 001–$15 000	1			*$10 001–$15 000*	0
	$15 001–$25 000	4			*$15 001–$25 000*	1
	$25 001–$35 000	3			*$25 001–$35 000*	2
	$35 001–$50 000	5			*$35 001–$50 000*	2
	$50 001–$75 000	13			*$50 001–$75 000*	10
	$75 001–$100 000	16			*$75 001–$100 000*	10
	$100 001–$150 000	40			*$100 001–$150 000*	21
	$150 001 or greater	58			*$150 001 or greater*	40
	Not reported	6			*Not reported*	3
T1 ARI score	*Average*	2.3		T1-T2	*Average*	1.9
	SD	2.3		Interval	*SD*	0.4
	Range	1–10			*Range*	1.2–3.8
				T2 ARI	*Average*	1.8
				score	*SD*	2.3
					Range	0–9

Notes. Sample size, male/female ratio, age at T1 (in years; average, standard deviation and range), Tanner stage at T1 (average, standard deviation and range), race/ethnic category and family income are listed for the cross-sectional and longitudinal samples. T1 ARI score (Affective Reactivity Index; average, standard deviation and range) is listed for the cross-sectional sample and interval between T1 and T2 (in years; average, standard deviation and range) is listed for the longitudinal sample.
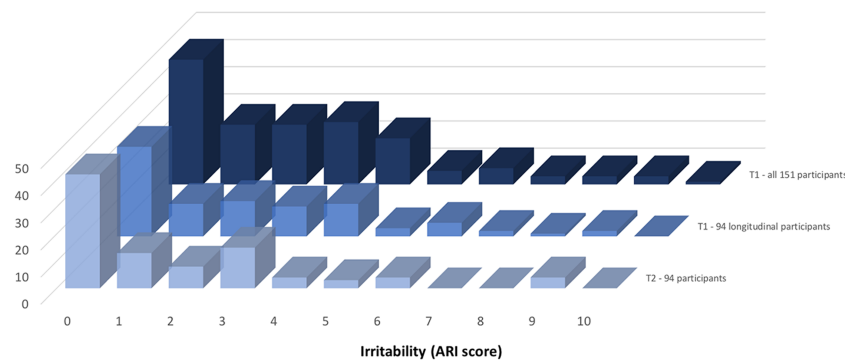

Fig. 2. Histograms showing distribution of ARI scores across sample. Shown are T1 scores across all 151 participants included in the cross-sectional analyses (dark blue, back), T1 scores among only those participants included in the longitudinal analyses (medium blue, middle) and T2 scores among the same longitudinal participants (light blue, front).

(Hua *et al.,* 2008; Hua *et al.,* 2009). Thirty participants, selected to be representative of the population, were used to make the minimal deformation template (MDT). This representative group was chosen semi-randomly by dividing the sample into tertiles based on exposure to early life stress and randomly selecting five females and five males from each tertile. The MDT is the template that deviates least from the anatomy of the participants

with respect to a mathematically defined metric of difference; in some circumstances, using an MDT can improve statistical power (Lepore *et al.,* 2007). The MDT serves as an unbiased registration target for nonlinear registrations.

For cross-sectional analyses, each participant's masked, non-uniformity-corrected, template-aligned T1-weighted image was non-linearly aligned to the MDT, using Advanced Normaliza-

tion Tools' Symmetric Normalization (SyN; Avants, Epstein, Grossman, and Gee, 2008). SyN registration used a multi-level approach, i.e. the 'moving' and fixed T1-weighted images were successively less smoothed at each level, with a full resolution registration occurring at the final level. We used 150, 80, 50 and 10 iterations at each level, with a Gaussian kernel smoothing sigma set to 3, 2, 1 and 0, respectively (7.05, 4.7, 2.35 and 0 voxels full width at half maximum) and shrink factors of 4, 2, 2 and 1, respectively. Image similarity was measured using the ANTs implementation of mutual information (Avants *et al.,* 2011). Image intensities were winsorized, excluding top and bottom 1% of voxels, and histogram matching was used. The output Jacobian determinant image showed the direction and magnitude of volume difference between the participant's T1 and the MDT. For longitudinal analyses, each participant's template-aligned T1 from the follow-up scan was non-linearly aligned to the template-aligned T1 from the first scan using the same parameters listed above. The output Jacobian determinant image showed the direction and magnitude of the change between the participant's Time 1 and Time 2 anatomical images. Output was visually checked for quality.

Statistical analyses

In our voxel-wise linear regression testing for associations with irritability, we included intracranial volume (ICV) as a covariate. The 9-DOF linear registration that is part of our processing protocol accounts for differences in overall brain scale, removing much of the effect of ICV; nevertheless, we included ICV, computed from the linearly registered image, as a covariate. We also ran models without ICV, reported in Supplementary Tables S2–S4. To test associations with irritability, we conducted several models assessing concurrent and predictive associations between irritability and brain volume:

Model 1 (Cross-sectional association at T1):

$$X_{T1} \sim A + \beta_{ARI\_T1}ARI\_T1 + \beta_{ageT1}AgeT1 + \beta_{Tanner_{T1}}TannerT1$$
$$+ \beta_{sex}Sex + \beta_{Race}Race + \beta_{ICVT1}ICVT1 + \varepsilon$$

Model 2 (T1 brain structure predicting change in irritability):

$$X_{T1} \sim A + \beta_{ARI\_\Delta}ARI\_\Delta + \beta_{ageT1}AgeT1 + \beta_{Interval}Interval$$
$$+ \beta_{Tanner_{T1}}TannerT1 + \beta_{Tanner_\Delta}Tanner\Delta$$
$$+ \beta_{Sex}Sex + \beta_{Race}Race + \beta_{ICVT1}ICVT1 + \varepsilon$$

Model 3 (T1 irritability predicting change in brain structure):

$$X_\Delta \sim A + \beta_{ARI\_T1}ARI\_T1 + \beta_{ageT1}AgeT1 + \beta_{Interval}Interval$$
$$+ \beta_{Tanner_{T1}}TannerT1 + \beta_{Tanner_\Delta}Tanner\Delta + \beta_{Sex}Sex$$
$$+ \beta_{Race}Race + \beta_{ICVT1}ICVT1 + \varepsilon$$

Model 4 (Longitudinal changes in irritability and brain structure):

$$X_\Delta \sim A + \beta_{ARI\_\Delta}ARI\_\Delta + \beta_{ageT1}AgeT1 + \beta_{Interval}Interval$$
$$+ \beta_{Tanner_{T1}}TannerT1 + \beta_{Tanner_\Delta}Tanner\Delta$$
$$+ \beta_{Sex}Sex + \beta_{Race}Race + \beta_{ICVT1}ICVT1 + \varepsilon$$

where X is the Jacobian determinant value at a given position, A is the constant Jacobian determinant term, the βs are the covariate regression coefficients and ε is an error term. When applicable, variables are noted as being measured at T1 or T2, or as a change from T1 to T2 (Δ). These models can be summarized as follows:

Model 1—the association between ARI and regional brain volume at T1;

Model 2—the association between regional brain volume at T1 and change in ARI score from T1 to T2;

Model 3—the association between T1 ARI and change in brain volume from T1 to T2;

Model 4—the association between change in ARI and change and brain volume from T1 to T2.

We used the 'lm()' function from the 'stats' package in R (https://stat.ethz.ch/R-manual/R-devel/library/stats/html/lm. html, version 2.9.2) to fit each model using linear regression voxel-wise. For each model, results were corrected for multiple comparisons across all voxels tested using Searchlight FDR [false discovery rate, $q < 0.05$ (Langers *et al.,* 2007)]. Searchlight FDR uses a sliding window approach to correct for multiple comparisons, yielding improved sensitivity over conventional FDR while maintaining the specificity of conventional FDR and FWE (family-wise error) approaches. We report only those clusters that exceeded 50 voxels. Covariates across the models included age, sex, Tanner stage, race/ethnicity, ICV, interval between T1 and T2 and change in Tanner stage between T1 and T2. We also ran models without pubertal stage, reported in Supplementary Tables S2–S4. For models 2 and 4, we additionally tested models including T1 ARI. A histogram of the change in ARI between T1 and T2 across our sample is presented in Supplementary Figure S1.

Results

Three of the four models tested yielded significant results. We present the results for each model below. Because space precludes a complete discussion of all of the clusters identified, we highlight specific clusters here and present all results in Tables 2–4.

Model 1: cross-sectional associations between irritability and regional brain volume at T1 (baseline)

The 151 participants provided data for Model 1, which yielded both positive and negative concurrent associations between ARI and brain volume at T1. Positive associations were fairly evenly split between gray matter (GM) and white matter (WM) and between hemispheres. Higher levels of irritability were associated with greater volume in the left dorsal ACC, left medial orbitofrontal cortex, left corpus callosum midbody, right hippocampus and right insula. Negative associations were skewed towards GM over WM. Higher levels of irritability were associated with smaller volume in a large cluster including the putamen and internal capsule and a number of frontal and occipital GM clusters. Clusters are shown in Table 2 and Figure 3.

Model 2: longitudinal associations between regional brain volume at T1 and change in irritability from T1 to T2

The 94 participants contributed data to Model 2. There were more positive than negative associations with left hemisphere

Table 2. Significant clusters from Model 1 (cross-sectional association at T1)

Positive							
Voxels	T-stat	X	Y	Z	Side	Structure	Tissue
2993	4.7	−7	40	13	L	Cingulate/cingulum	GM/WM
1193	3.67	−46	−19	−15	L	Middle temporal gyrus	WM
904	3.81	42	−37	19	R	Angular gyrus	WM
749	3.69	−39	23	21	L	Middle frontal gyrus	GM/WM
636	3.22	−48	−40	−6	L	Middle temporal gyrus	WM
564	3.51	−4	31	−24	L	Medial orbitofrontal cortex	GM
308	3.97	47	29	24	R	Middle frontal gyrus	GM
275	3.34	46	−17	−15	R	Middle temporal gyrus	WM
254	3.08	33	25	46	R	Middle frontal gyrus	GM/WM
224	3.46	65	−55	10	R	Fusiform gyrus	GM
192	3.47	44	−28	−13	R	Middle temporal gyrus	WM
172	3.49	52	46	−2	R	Inferior frontal gyrus	GM
155	3.65	34	8	5	R	Insula	GM
136	3.38	23	−6	−27	R	Hippocampus	GM
116	3.65	−14	−6	27	L	Corpus callosum	WM
104	3.65	−59	−27	22	L	Supramarginal gyrus	GM
85	3.62	34	50	33	R	Superior frontal gyrus	GM
Negative							
Voxels	T-stat	X	Y	Z	Side	Structure	Tissue
3789	−4.25	−33	26	10	L	Putamen/internal capsule	GM/WM
499	−3.96	−14	19	35	L	Superior frontal gyrus	WM
492	−4.36	42	−88	7	R	Lateral occipital gyrus	GM
409	−3.91	11	43	17	R	Superior frontal gyrus	GM
407	−3.84	43	30	−19	R	Inferior frontal gyrus	GM
404	−3.55	18	−69	0	R	Lingual gyrus	GM/WM
390	−3.27	31	−63	13	R	Posterior thalamic radiation	WM
319	−3.18	20	−66	−33	R	Cerebellum	WM
316	−3.59	−26	−66	−10	L	Lingual gyrus	GM
302	−4.71	−64	−7	23	L	Postcentral gyrus	GM
238	−3.65	−26	64	24	L	Superior frontal gyrus	GM
196	−3.86	−10	−74	−1	L	Lingual gyrus	GM
78	−3.35	25	13	−40	R	Temporal pole	GM
62	−4.25	−18	57	37	L	Superior frontal gyrus	GM
62	−3.55	−60	−49	4	L	Middle temporal gyrus	GM

Notes. Clusters showing an association between volume and irritability at T1. Shown are the cluster size, peak regression T-statistic, coordinates (MNI), hemisphere, structure and tissue type.

clusters, and more negative than positive associations with right hemisphere clusters. There were also more negative associations in GM than in WM. There were more associations, both positive and negative, with clusters in the frontal cortex than in other brain lobes. Individuals with greater baseline volume in the right caudate and left corpus callosum midbody had greater increases in irritability over time. Greater baseline volume in the cingulate gyrus, superior frontal gyrus and inferior frontal gyrus was associated with decreases in irritability over time. When we controlled for baseline irritability, the caudate, corpus callosum and cingulate clusters were no longer significant, but many of the frontal cortex clusters remained. Clusters are shown in Table 3 and Figure 4.

Model 3: longitudinal associations between irritability at T1 and change in regional brain volume from T1 to T2

The 94 participants contributed data to Model 3. Both positive and negative associations were balanced between GM and WM;

negative associations were skewed towards the left hemisphere. Participants who had higher levels of irritability at T1 had greater increases in volume in the left anterior *corona radiata*, left internal capsule and a number of frontal GM and WM clusters. Higher levels of irritability at T1 were also associated with less expansion, or more contraction, in the left caudate, left insula and a number of frontal GM and WM clusters. Clusters are shown in Table 4 and Figure 5.

Model 4: longitudinal associations between change in irritability and change in regional brain volume from T1 to T2

No results survived multiple comparisons correction for Model 4.

Overlap among models

To identify brain regions that were associated consistently with irritability in the three significant models, we overlaid the pos-

Table 3. Significant clusters from Model 2 (volume at T1 predicting changes in irritability)

				Positive			
Voxels	T-stat	X	Y	Z	Side	Structure	Tissue
683	4.41	−24	−23	58	L	Precentral gyrus	GM
430	3.33	−55	−35	7	L	Superior temporal gyrus	GM
416	3.23	16	22	−1	R	Caudate	GM
347	4.15	−15	39	38	L	Superior frontal gyrus	GM
207	3.84	−10	15	19	L	Corpus callosum	WM
181	3.84	−16	−13	49	L	Superior frontal gyrus	WM
116	3.58	−13	−38	50	L	Superior parietal lobule	GM/WM
85	3.46	−14	19	36	L	Superior frontal gyrus	WM
83	4.80	−10	−96	16	L	Cuneus	GM
69	3.29	31	27	−10	R	Inferior frontal gyrus	GM/WM

				Negative			
Voxels	T-stat	X	Y	Z	Side	Structure	Tissue
674	−3.90	40	8	17	R	Insula/Inferior frontal gyrus	GM/WM
445	−4.25	47	24	19	R	Inferior frontal gyrus	GM/WM
414	−3.72	41	−30	13	R	Transverse temporal gyrus	GM
233	−3.81	−28	−48	34	L	Superior parietal lobule	GM
221	−4.35	−6	−91	30	L	Cuneus	GM
127	−4.05	0	−13	25	R	Cingulate	GM
121	−3.75	39	−55	35	R	Angular gyrus	GM/WM
108	−3.70	55	−4	34	R	Precentral gyrus	GM
105	−3.86	6	66	5	R	Superior frontal gyrus	GM
80	−3.66	36	54	22	R	Superior frontal gyrus	GM
75	−4.15	−4	66	25	L	Superior frontal gyrus	GM

				Including T1 ARI in model			
				Positive			
Voxels	T-stat	X	Y	Z	Side	Structure	Tissue
409	4.04	−15	39	38	L	Superior frontal gyrus	GM/WM
231	3.39	−48	−35	0	L	Superior temporal gyrus	GM/WM
208	5.46	−10	−96	16	L	Cuneus	GM
127	3.91	−16	−14	48	L	Superior frontal gyrus	WM
105	4.12	−13	44	23	L	Superior frontal gyrus	WM
51	3.62	−48	1	16	L	Precentral gyrus	WM

				Negative			
Voxels	T-stat	X	Y	Z	Side	Structure	Tissue
214	4.91	−6	−91	30	L	Cuneus	GM
201	3.78	39	6	16	R	Inferior frontal gyrus	WM
98	3.98	8	64	6	R	Superior frontal gyrus	GM
90	5.05	−3	66	25	L	Superior frontal gyrus	GM
79	3.91	−38	−88	15	L	Lateral occipital gyrus	GM
54	3.87	31	49	17	R	Middle frontal gyrus	GM

Notes. Clusters showing an association between baseline volume and changes in ARI. Shown are the cluster size, peak regression T-statistic, coordinates (MNI), hemisphere, structure and tissue type.

itive and negative associations across models to create 'heat maps' that indicated which voxels were identified by more than one model. Although most of the clusters were significant in only one model, some clusters emerged in two or three of the models. There was overlap between positive associations in Model 1 and negative associations in Models 2 and 3 in the WM of the left MFG. This overlap indicates that higher baseline irritability is associated with greater baseline volume in the left MFG but with smaller increases in volume over time, and that greater baseline volume in the left MFG is associated with smaller increases in irritability over time. There was also overlap between positive associations in Model 3 and negative associations in Model 1 in a large cluster that included the left internal capsule, indicating that higher irritability at T1 is associated with smaller volumes in these regions initially, but with greater expansion in these areas over time. There was overlap between positive associations in Model 1 and negative associations in Model 2 in the WM of the angular gyrus and GM of the right MFG, indicating that higher baseline irritability is associated with greater baseline volume in the right MFG and right angular gyrus, but with smaller increases in volume over time. Finally, there was overlap between positive associations

Table 4. Significant clusters from Model 3 (T1 irritability predicting change in brain structure)

			Positive				
Voxels	T-stat	X	Y	Z	Side	Structure	Tissue
494	3.8	−17	14	5	L	Anterior internal capsule	WM
467	4.26	−16	−12	2	L	Posterior internal capsule	WM
224	4.27	19	14	54	R	Superior frontal gyrus	WM
104	3.35	−21	22	22	L	Anterior corona radiata	WM
86	3.86	26	51	34	R	Superior frontal gyrus	GM
83	4.37	41	−7	56	R	Precentral gyrus	GM
69	4.43	−67	−18	−6	L	Middle temporal gyrus	GM
59	5.04	−61	−11	36	L	Postcentral gyrus	GM

			Negative				
Voxels	T-stat	X	Y	Z	Side	Structure	Tissue
512	−4.16	−33	2	−1	L	Insula	GM
337	−3.95	20	−67	−13	R	Cerebellum	GM
285	−4.31	17	66	9	R	Superior frontal gyrus	GM/WM
252	−4.16	−9	10	13	L	Caudate	GM
198	−4.44	−41	23	32	L	Middle frontal gyrus	GM/WM
183	−4.48	−10	17	50	L	Superior frontal gyrus	WM
119	−3.94	−42	20	22	L	Middle frontal gyrus	GM
92	−4.30	−54	−18	−14	L	Middle temporal gyrus	WM
88	−3.37	−12	3	18	L	Caudate	GM
83	−4.69	−43	2	28	L	Precentral gyrus	GM
70	−4.05	36	−15	25	R	Postcentral gyrus	WM
62	−4.19	−44	−18	32	L	Postcentral gyrus	WM
56	−4.26	−41	38	19	L	Middle frontal gyrus	WM

Notes. Clusters showing an association between irritability at T1 and change in volume. Shown are the cluster size, peak regression T-statistic, coordinates (MNI), hemisphere, structure and tissue type.

in Model 2 and negative associations in Model 1 in the superior *corona radiata* and lateral occipital gyrus, indicating that higher baseline irritability is associated with smaller baseline volume in these areas, but with greater volume expansion over time. These clusters are presented in Figure 6 and Supplementary Figure S2.

Discussion

This study examined cross-sectional and longitudinal associations between irritability and regional brain volume in a community sample from earlier to later adolescence. Few studies have examined neural correlates of irritability (including SMD and DMDD) in relation to variation in brain structure. Irritability was associated with altered brain volume in a number of striatal, limbic and limbic-associated structures. Most of the brain areas that were positively associated with irritability, either at baseline or longitudinally, typically decrease in volume over the developmental period studied here, suggesting that irritability is associated with delayed brain maturation.

We found larger baseline volumes in a number of fronto-striatal structures in individuals with higher levels of irritability. Cross-sectionally, higher levels of irritability were associated with greater volume of the hippocampus, dorsal ACC/cingulum, medial OFC and insula and with smaller volume in the putamen, internal capsule and a number of GM clusters across the brain. It is noteworthy that the hippocampus, ACC and mOFC are part of, or closely integrated with, the limbic system. The limbic system is central to emotion regulation, and traditionally is conceptualized as including the amygdala, hippocampus, hypothalamus, cingulate cortex, parahippocampal cortex,

cingulum bundle and fornix, although this is not a universally accepted set of structures (Nieuwenhuys, 2007; Rajmohan and Mohandas, 2007). Some neuroanatomists include the OFC in the limbic system, as it has structural and functional connectivity with canonical limbic system structures (Rajmohan and Mohandas, 2007). Lesion studies in humans and non-human primates have reported a link between irritability and limbic system functioning (Eichelman, 1983). Prior structural studies of irritability have similarly reported altered volume in frontal regions (Adleman *et al.*, 2012; Gold *et al.*, 2016). In the present study, across both models of cross-sectional brain volume (Models 1 and 2), far more GM than WM clusters were negatively associated with irritability; thus, smaller GM volumes were associated both with higher baseline irritability and with greater increases in irritability over time. Positive associations with irritability were more balanced between GM and WM. Typically, GM volume decreases and WM volume increases throughout childhood and adolescence, although these trajectories vary across the brain (Gogtay *et al.*, 2004). In our sample, the vast majority of the brain areas in which there was a positive association between volume and irritability at baseline decreased in volume over the study period (regional changes in brain volume over time across the whole group shown in Figure 7). Against this background, our finding of larger volumes in individuals with higher levels of irritability could indicate delayed maturation, as the age-expected decreases in volume are lagging (Mills *et al.*, 2016; Tamnes *et al.*, 2017). Clusters in which there was a negative association between baseline volume and irritability were more evenly divided between areas that are increasing and areas that are decreasing in volume over this period. Without additional earlier scans, we cannot
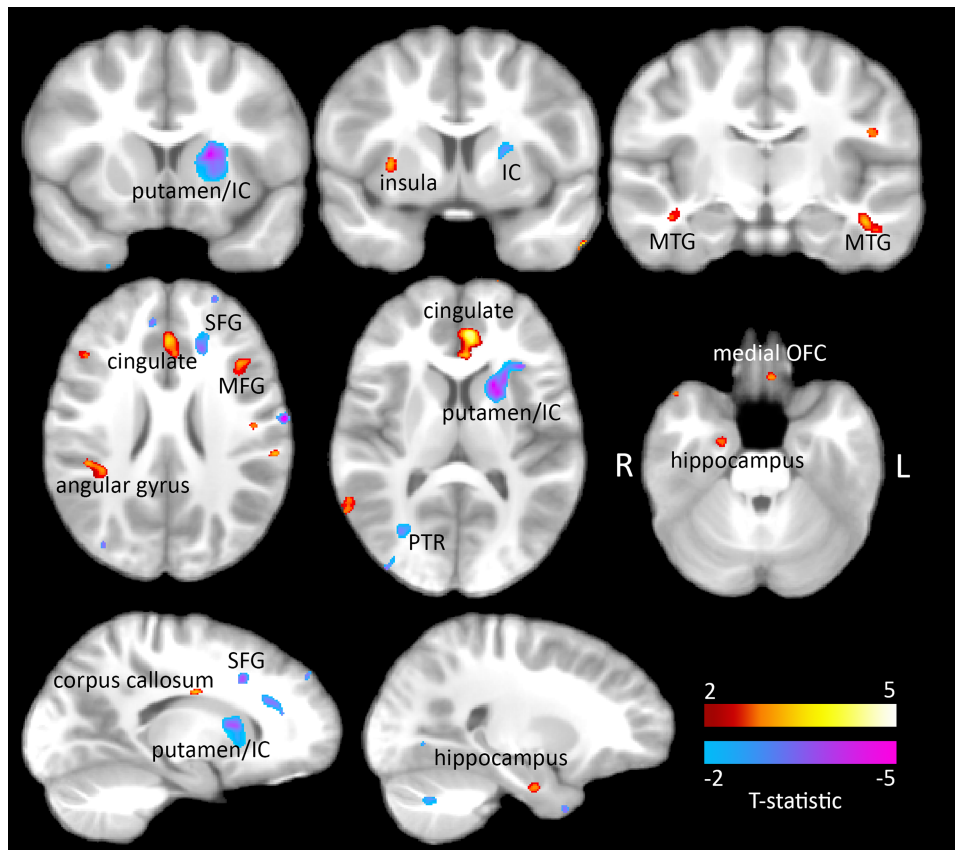
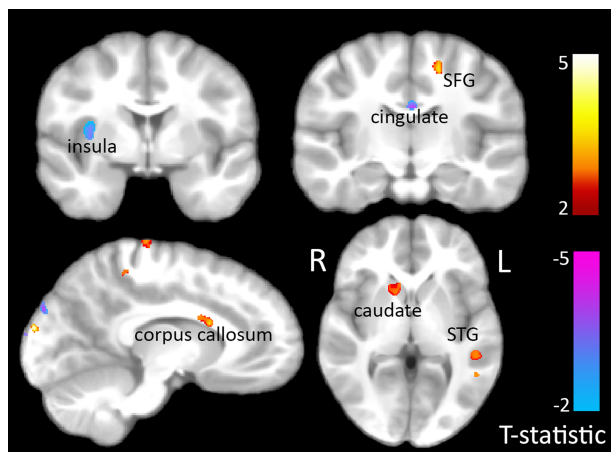**Fig. 3**. Significant results from cross-sectional imaging analyses (Model 1). Results from Model 1 are shown—those involving cross-sectional brain imaging with cross-sectional irritability scores. Red-yellow are those showing positive associations, blue-purple are clusters showing negative associations. IC = internal capsule, MTG = middle temporal gyrus, SFG = superior frontal gyrus, MFG = middle frontal gyrus, PTR = posterior thalamic radiation, OFC = orbitofrontal cortex. Images are in radiological convention, with the left hemisphere on the right side of the image.

Fig. 4. Significant results from cross-sectional imaging + longitudinal irritability analyses (Model 2). Results from Model 2 are shown—those involving cross-sectional brain imaging with longitudinal irritability scores. Red-yellow are those showing positive associations, blue-purple are clusters showing negative associations. SFG = superior frontal gyrus, STG = superior temporal gyrus. Images are in radiological convention, with the left hemisphere on the right side of the image.

determine conclusively whether these effects indicate delayed maturation or irritability-related differences that emerged earlier in childhood. Further, although we cannot determine

the degree to which these structural alterations contribute to, rather than result from, higher levels of irritability, our results indicate that structural alterations commonly seen in individuals with clinically significant irritability (Adleman *et al., 2012*; Gold *et al., 2016*) are also evident when examining the transdiagnostic construct of irritability as a continuous variable.

Longitudinally, we examined areas in which subsequent neural expansion or contraction was associated with irritability at T1. Higher irritability at T1 was associated with greater volume expansion, or less contraction, in the internal capsule and anterior corona radiata, and with less expansion, or more contraction, in the caudate and a number of frontal clusters. Among clusters in which there was a positive association between baseline irritability and changes in brain volume, all were in areas that typically decrease in volume over this developmental period. This pattern of findings suggests delayed development, given that individuals with higher levels of irritability exhibited less volume contraction across these areas. Clusters showing a negative association between baseline irritability and volume changes were balanced between those increasing and decreasing in volume over time. The volume of the left caudate peaks around age 9 and then decreases (Dima *et al., 2015*), suggesting that individuals with higher levels of irritability are losing caudate volume more rapidly than are their less irritable peers. The caudate has been found to have both smaller volume and hypoactivation in depressed
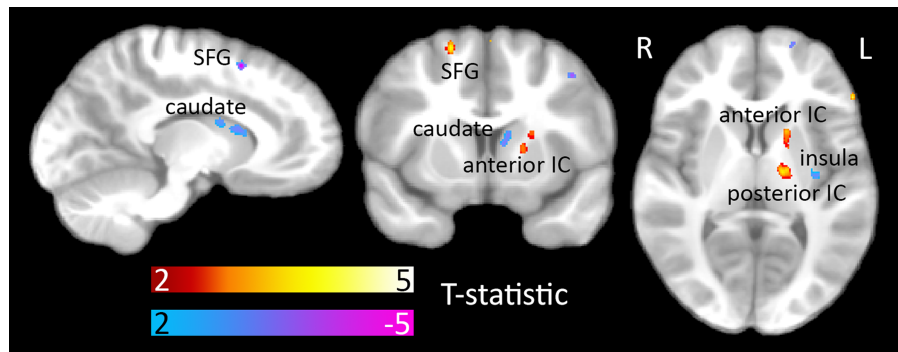
Fig. 5. Significant results from longitudinal imaging analysis (Model 3). Results from Model 3 are shown—those involving longitudinal brain imaging with cross-sectional irritability scores. Red-yellow are those showing positive associations, blue-purple are clusters showing negative associations. SFG = superior frontal gyrus, IC = internal capsule. Images are in radiological convention, with the left hemisphere on the right side of the image.
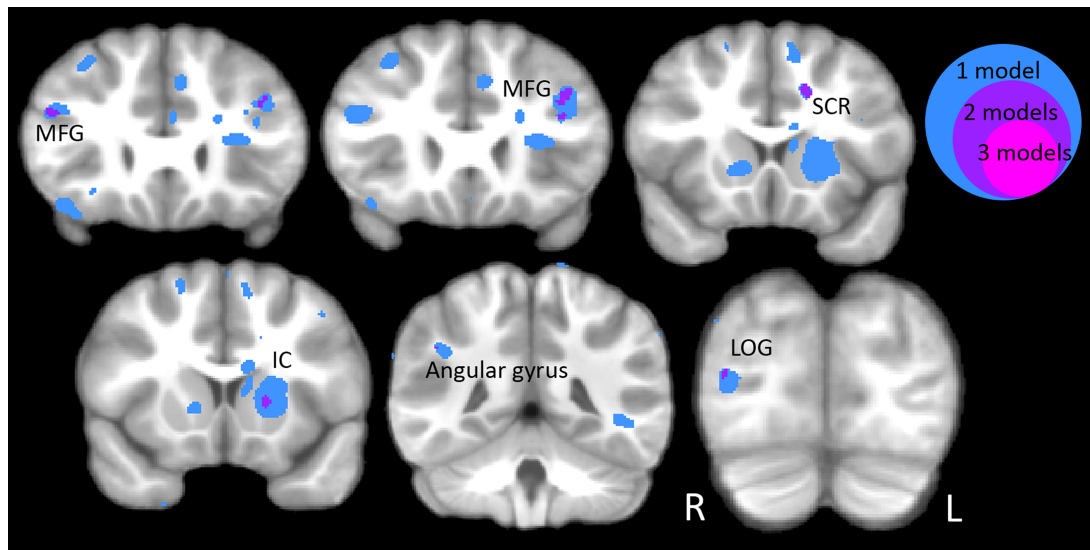

Fig. 6. Overlap in results across models. Positive and negative associations found across all seven models are overlaid to show overlap. Several areas of overlap are noted. Blue clusters were reported in one model, purple clusters in two models and pink clusters in three models, as shown in the legend. MFG = middle frontal gyrus, SCR = superior corona radiata, IC = internal capsule, LOG = lateral occipital gyrus. Images are in radiological convention, with the left hemisphere on the right side of the image.
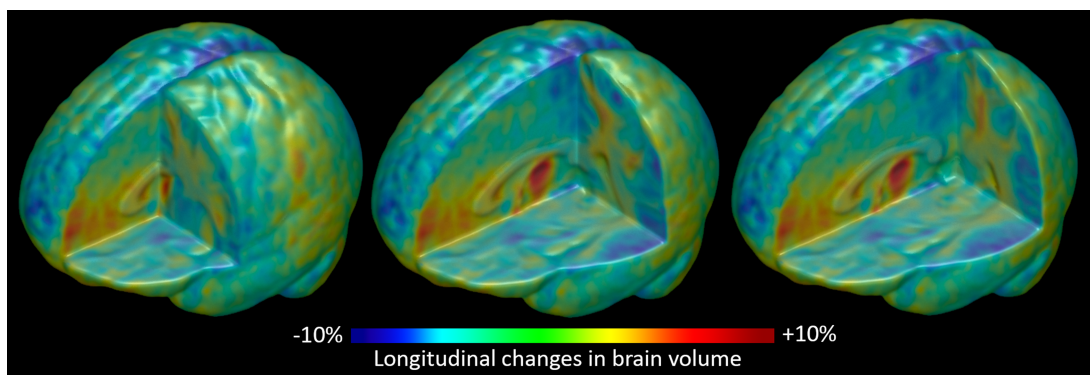

Fig. 7. Longitudinal changes in brain volume across the sample. The images representing change over time for each participant (the Jacobian determinant) were averaged across the group to show age-related changes in the sample as a whole to provide context for our results. The direction and magnitude of the changes are indicated by the color, shown in the color bar, with blue indicating areas of volume contraction and red areas of volume expansion.

individuals (Krishnan *et al.,* 1992; Pizzagalli *et al.,* 2009). While these areas have not been implicated in previous studies of irritability and brain structure, studies of brain function in clinical populations have reported decreased activation in the striatum in response to frustration (Deveney *et al.,* 2013; Perlman *et al.,* 2015). We found that more irritable individuals had smaller baseline volume in the putamen and more volume loss in the caudate, suggesting that striatal disruption is present even when examining irritability in a non-clinical sample.

The longitudinal nature of this study yields insights concerning the association between irritability and structural brain development; further follow-up is necessary, however, to determine whether more irritable individuals are simply lagging behind their less irritable counterparts in brain development and will ultimately catch up, or alternatively, will never reach their age-expected targets. Examining the overlap in significant clusters across the models examined in this study provides insight about the temporal nature of the association between regional brain volume and irritability. We found that individuals with higher baseline irritability had larger baseline volume in the bilateral MFG and right angular gyrus, and smaller baseline volume in the internal capsule, superior *corona radiata* and lateral occipital gyrus. Individuals with higher baseline irritability were more likely to show less volume contraction in the left internal capsule and more volume contraction in the left MFG. Individuals with larger baseline volume in the lateral occipital gyrus and superior *corona radiata* were more likely to have increased irritability over time, while those with larger baseline volume in the right angular gyrus and bilateral MFG were more likely to have decreased irritability over time. We should note three limitations of this study. First, we measured irritability through parent report; in future studies, data from other informants, such as teachers, will be important in corroborating parents' reports of their children's irritability. Second, investigators have found a floor effect for the ARI in community samples (Stoddard *et al.,* 2014); in our sample, too, although we had a reasonable range of scores on the ARI, the majority of participants clustered around a similar value near the floor of the ARI. Although we excluded participants with extreme ARI scores (>3 SD), it is nevertheless possible that the significant associations reported here are driven in part by a smaller subset of participants with higher scores on this measure. In future research, the ARI should be augmented by other measures of irritability.

Finally, as presented in Table 1, we studied a volunteer community sample of adolescents; not surprisingly, the mean irritability score in this sample was lower than has been reported in clinical samples (Stoddard *et al.,* 2017; Kircanski *et al.,* 2018; Tseng *et al.,* 2018).

Despite these limitations, the present findings are important in identifying brain structural correlates of irritability in a sample of young adolescents; these structural differences may be precursors to future internalizing and externalizing disorders. Identifying these risk factors is critical to understanding the emergence of dysfunction and is an important first step in developing more effective interventions. Investigators should continue to conduct longitudinal research to determine whether these alterations predict the development of psychopathology and other adverse outcomes.

Supplementary data

Supplementary data are available at *SCAN* online.

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