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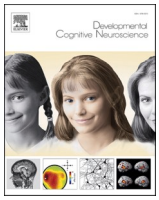

Irritability in early to middle childhood: Cross-sectional and longitudinal associations with resting state amygdala and ventral striatum connectivity

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ABSTRACT

Background: Irritability is a common symptom that may affect children's brain development. This study aims to (1) characterize age-dependent and age-independent neural correlates of irritability in a sample of 4–8 year old children, and (2) examine early irritability as a predictor of change in brain connectivity over time.
Methods: Typically developing children, ages 4–8 years, with varying levels of irritability were included. Resting state fMRI and parent-rated irritability (via Child Behavior Checklist; CBCL) were collected at up to three time points, resulting in a cross-sectional sample at baseline ($N = 176$, $M = 6.27$, $SD = 1.49$), and two subsamples consisting of children who were either 4 or 6 years old at baseline that were followed longitudinally for two additional timepoints, one- and two-years post-baseline. That is, a "younger" cohort (age 4 at baseline, $n = 34$, M age $= 4.44$, $SD = 0.25$) and an "older" cohort (age 6 at baseline, n = 29, M age $= 6.50$, $SD = 0.30$). Across our exploratory analyses, we examined how irritability related to seed-based intrinsic connectivity via whole-brain connectivity ANCOVAs using the left and right amygdala, and left and right ventral striatum as seed regions.
Results: Cross-sectionally, higher levels of irritability were associated with greater amygdala connectivity with the posterior cingulate, controlling for child age. No age-dependent effects were observed in the cross-sectional analyses. Longitudinal analyses in the younger cohort revealed that early higher vs. lower levels of irritability, controlling for later irritability, were associated with decreases in amygdala and ventral striatum connectivity with multiple frontal and parietal regions over time. There were no significant findings in the older cohort.
Conclusions: Findings suggest that irritability is related to altered neural connectivity during rest regardless of age in early to middle childhood and that early childhood irritability may be linked to altered changes in neural connectivity over time. Understanding how childhood irritability interacts with neural processes can inform pathophysiological models of pediatric irritability and the development of targeted mechanistic interventions.

1. Introduction

Irritability, defined as a lower threshold for anger relative to peers (Brotman et al., 2017), is extremely common in early and middle childhood (i.e., preschool to school age) and a primary reason parents seek psychiatric treatment for their children (Peterson et al., 1996). Indeed, irritability is present in both typically and atypically developing populations and is a dimensional symptom cross-cutting multiple psychological disorders, including anxiety, depressive and bipolar disorders, oppositional defiant disorder (ODD), and disruptive mood dysregulation disorder (DMDD; Dougherty et al., 2015; Stringaris, 2011). Irritability, in childhood in particular, is associated with concurrent impairment, greater service use, and worse academic performance (Dougherty et al., 2015). Despite a normative decline in irritability from early to middle childhood (Copeland et al., 2015), irritability levels persist in up to half of children who present with elevated irritability in early childhood (Wiggins et al., 2018, 2014). Indeed, such persistence of irritability from early to middle childhood predicts worse outcomes in adulthood, including anxiety and depression, suicidality, and lower socioeconomic attainment (Brotman et al., 2006; Copeland et al., 2014; Stringaris et al., 2009; Vidal-Ribas et al., 2016). Despite the prevalence and consequences of irritability

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symptoms in early to middle childhood, little is known about the neurodevelopmental course of irritability during this growth period. Understanding how irritability interacts with neurodevelopmental processes in this early to middle childhood period may facilitate mechanism-based prevention approaches to head off detrimental downstream consequences of childhood irritability.

Theoretical models of irritability have proposed threat and reward processing as key pathophysiological mechanisms underlying irritability, involving neural dysfunction in amygdala, striatal, prefrontal, and parietal networks (Brotman et al., 2017). Task-based neuroimaging studies of youth with elevated levels of irritability have accumulated evidence for altered threat and reward processing implicating these networks (e.g., Brotman et al., 2017; Deveney et al., 2013; Kryza-Lacombe et al., 2021). For example, irritability in adolescents is associated with alterations in amygdala activation when labeling ambiguous emotional faces (Wiggins et al., 2016), as well as altered striatal activation and amygdala and ventral striatum connectivity when missing vs. receiving rewards (Kryza-Lacombe et al., 2021). Most of the extant work on neural mechanisms has been in children between middle childhood and adolescence. Only a handful of studies have thus far provided evidence for irritability-related alterations in these networks in early to middle childhood: One study showed that irritability in 6–9-year-olds was related to decreased striatal and prefrontal activation during a frustration task (Perlman et al., 2015). Another study demonstrated that preschool irritability predicted altered amygdala-insula and frontostriatal connectivity during a reward task 3 years later and that irritability in middle childhood was concurrently associated with amygdala and striatal connectivity with prefrontal and posterior structures respectively (Dougherty et al., 2018). Finally, previous work also demonstrated an age-related increase in amygdala activation among highly irritable children aged 4–12 when viewing negative emotional video clips (Karim and Perlman, 2017).

In addition to the many fMRI studies that probed threat and reward processes directly via tasks, resting state fMRI, which measures intrinsic functional connectivity patterns in the brain when not doing any task in particular (i.e., "at rest"), may also provide insight into the neural underpinnings of irritability. In line with theoretical models of irritability that highlight the amygdala and ventral striatum as potentially implicated in irritability (Brotman et al., 2017), extant empirical work suggests that threat and reward networks subserved by these regions are active during rest (Kinnison et al., 2012; Wang et al., 2010). Two previous studies documented associations between pediatric irritability and resting state functional connectivity, and found increased amygdala connectivity with the medial prefrontal pole among highly irritable adolescents compared to non-irritable youths (Stoddard et al., 2015) and aberrant anterior midcingulate cortex connectivity with the precuneus among children aged 5–9 years with severe temper outbursts compared to controls (Roy et al., 2018). Resting state fMRI methods are particularly useful for studying neurodevelopment in younger children because younger children vary widely in their ability to reliably perform the tasks used to probe psychological processes. Additionally, intrinsic functional connectivity may be especially important to examine in light of theoretical (Johnson, 2000) and empirical (Riggins et al., 2016) work suggesting that brain development throughout childhood may be less of a function of specific regional maturation, but instead the organization of connectivity between relevant brain regions.

Neurodevelopmental models (e.g., Di Martino et al., 2014; Grayson and Fair, 2017) suggest that developmental changes and aberrancies in resting-state functional connectivity can be linked to the onset of psychiatric disorders. Given the normative decline in irritability from early to middle childhood, deviations from normative irritability levels may relate to abnormal brain development (i.e., changes in neural connectivity) that makes children vulnerable to developing mood disorders and related psychopathology. Better understanding how the brain (re)organizes itself through changes in intrinsic functional connectivity across early and middle childhood may help elucidate the onset and cascade of psychopathology, and inspire the development of new, more targeted, mechanistic treatments. It is therefore important to understand how irritability interacts with neurodevelopment in early childhood, especially longitudinally (i.e., how does irritability relate to changes in brain connectivity as children age?). Only a few studies have investigated longitudinal neural changes associated with irritability and focused not on functional but structural changes (i.e., Adleman et al., 2012; Dennis et al., 2019; Pagliaccio et al., 2018). Specifically, these studies found evidence for aberrant brain structure in those with elevated irritability. Dennis et al. (2019) and Pagliaccio et al. (2018) found that higher levels of irritability were associated with increased volume (e.g., medial orbitofrontal cortex, cingulate cortex) and increased gray matter (e.g., left superior temporal gyrus), respectively. However, Dennis et al. (2019) and Adleman et al. (2012) also found elevated irritability related to decreased volume in others (e.g., insula, right superior/inferior parietal lobule). Evidence also suggested that delayed brain maturation was associated with irritability (i.e., typical volume decreases associated with development were delayed in individuals with higher levels of irritability; Dennis et al., 2019).

The goal of the present exploratory study was to begin to characterize the relations between dimensionally-measured irritability and (changes in) resting state connectivity in reward/emotion networks across early to middle childhood. To maximize sample size yet still investigate longitudinal associations, we leveraged a cross-sectional sample with two subsamples that were followed longitudinally for two additional timepoints, one- and two-years post-baseline: a younger cohort (age 4 at baseline and reassessed at age 5 and 6) and an older cohort (age 4 at baseline and reassessed at age 7 and 8). Parents reported on child irritability symptoms using the Child Behavior Checklist (CBCL) at each assessment and children underwent resting state fMRI. We had two aims: Aim 1 examined the relation between parent-reported irritability and children's resting-state connectivity cross-sectionally at baseline, including age-dependent and age-independent effects. Aim 2 evaluated how early irritability, above and beyond later irritability, relates to changes in neural connectivity over time in two longitudinal cohorts followed annually over three years (younger cohort: ages 4 to 6; older cohort: ages 6 to 8). We did not have directional hypotheses, because the literature does not clearly support either increased or decreased connectivity in relation to irritability (Kryza-Lacombe et al., 2021; Roy et al., 2018) and moreover due to the highly novel aspects of our study (i.e., the first longitudinal study of irritability-related brain connectivity and the first resting state connectivity study in such a young sample).

2. Methods

This protocol was reviewed and approved by the University of Maryland Institutional Review Board. Parents gave written informed permission and minor participants provided assent prior to administering study materials and fMRI data acquisition.

2.1. Participants

Participants ($N = 200$; $n = 100$ female) ages 4–8 years old ($M = 6.2$, $SD = 1.5$) were recruited from the from the greater Baltimore-Washington area through the Infant and Child Studies Consortium, a multi-disciplinary research group at the University of Maryland, flyers, and word of mouth for a longitudinal study aimed at examining brain and memory development in early childhood (Geng et al., 2021; Riggins et al., 2018). For full recruitment procedures, see (Riggins et al., 2018).

Of the 200 participants recruited for the original study, 24 participants were excluded from the present study for one or more of the following reasons: missing resting state scans, missing irritability data at one or more timepoints, and/or excessive head motion (see below). At baseline, there were five cohorts: those that started at age 4, age 5, age 6, age 7, and age 8. Only the 4-year- and 6-year- old cohorts (i.e., the

younger and older cohorts in the present study) were followed over time. The final sample, at baseline, consisted of 176 children ages 4–8 years (*M* age = 6.27, *SD* = 1.49) and was used for our cross-sectional analyses. Two subsets of children, stratified for age, i.e., a younger cohort that was initially ~4 years old (at baseline: n = 34; *M* age = 4.44, *SD* = 0.25) and an older cohort that was initially ~6 years old (at baseline: n = 29; *M* age = 6.50, *SD* = 0.30), were longitudinally followed for two more time points (i.e., 1 and 2 years after baseline). The younger cohort had 8.8% attrition from baseline to time 3, and the older cohort had 10.4% attrition.

2.2. Measures

2.2.1. Irritability

Irritability was measured dimensionally using an empirically-derived irritability factor scale from the parent-reported Child Behavior Checklist (CBCL) (Stringaris et al., 2012; Wiggins et al., 2014). This scale has been previously validated (Evans et al., 2020; Wiggins et al., 2014) and comprises 3 items ("stubborn, sullen, or irritable," "sudden changes in mood or feelings," "temper tantrums or hot temper"), rated on a scale from 0 to 2 (0 = *Not true*, 1 = *Somewhat or Sometimes True*, 2 = *Very True or Often True*) over the past 6 months. Developmentally appropriate versions of the CBCL, ages 6–18 years (Achenbach and Rescorla, 2001) and ages 1.5–5 years (Achenbach and Rescorla, 2000), were used based on age; irritability items were identical across both versions. This subscale has been shown to have acceptable psychometric properties (alpha = 0.73; Evans et al., 2020; Stringaris et al., 2012; Wiggins et al., 2014). Additionally, CBCL irritability subscale scores for ages 6–18 years and ages 1.5–5 years have previously been used to measure changes across time (Wiggins et al., 2014). Irritability was assessed at baseline (alpha = 0.68) and each follow-up. Non-irritable depression and anxiety symptom measures were used to assess potential confounding impact of current symptoms on the observed resting state MRI findings. See Supplemental Materials for more information on additional measures (i.e., non-irritable depression, anxiety).

2.2.2. Neuroimaging acquisition

Prior to the MRI scan, children were trained in a mock scanner to acclimate them to the scanning environment. Anatomical and resting state functional brain images were acquired using a 3.0-T Siemens MRI scanner with a 12-channel head coil at baseline and each follow-up. High-resolution structural images for coregistration with functional images were acquired with a T1-weighted magnetization prepared rapid gradient echo sequence: TR = 1.9 s; TE = 2.32 ms; slice thickness = 0.9 mm with no gap; voxel size = 0.9 × 0.9 × 0.9 mm; matrix = 256 × 256 mm; flip angle = 9° field of volume = 230 * 23 mm, with a duration of 4 min and 26 s. For the resting state scan, a total of 210 whole-brain images were collected using a T2 * -weighted gradient-echo echo-planner imaging sequence (TR = 2 s, TE = 25 ms, slice thickness = 3.5 mm, voxel size = 3.0 ×3.0 ×3.5 mm, voxel matrix = 64 ×64, flip angle=70°, field of view = 192 mm, 36 slices), with a duration of 7 min and 6 s. The first four volumes were discarded to allow the scanner to reach steady state. During the resting state scan, children were told to lie as still as possible with their eyes open, while watching "Inscapes," a movie paradigm designed for collecting resting-state fMRI data to reduce potential head motion in children (Vanderwal et al., 2015).

2.3. Analytic plan

2.3.1. fMRI data preprocessing

Standard preprocessing procedures were completed using Analysis of Functional Neuroimages (AFNI; http://afni.nimh.nih.gov/afni/). Preprocessing steps included functional image realignment, censoring of image pairs with frame-wise displacement > 0.5 mm, slice-time correction, spatial smoothing (FWHM = 4 mm), and non-linear registration for spatial standardization to the Talairach template. Attempted use of a pediatric template (i.e., Haskins Pediatric template) resulted in poor spatial standardization. Resting state scans with mean frame-wise displacement (head motion) of ≥ 0.30 mm or censoring of ≥ 35% of image volumes were excluded from analyses (n = 12).

2.3.2. Individual-level connectivity

The left and right ventral striatum and left and right amygdala were used as connectivity seeds given evidence that neural circuity related to these areas is particularly vulnerable to alterations in early childhood (Fareri et al., 2015; Gabard-Durnam et al., 2014) and is implicated in irritability as documented in task-based connectivity studies (e.g., Dougherty et al., 2018; Hodgdon et al., 2021; Kryza-Lacombe et al., 2021). Unilateral seeds were chosen in order to detect the laterality of potential associations. Voxel-wise whole-brain resting state functional connectivity was calculated for each individual for each of four seed regions (left and right amygdala, left and right ventral striatum, defined by the Talairach template in AFNI). First, the BOLD time series for all voxels within each seed region were extracted and averaged, and then the correlation between each seed and the rest of the brain was calculated. Correlation values were converted to z scores via Fishers r-to-z transformation.

2.3.3. Group-level analyses

We utilized AFNI's 3dMVM program to estimate whole-brain ANCOVA models to address each research question. Models were run for each of the four seeds separately (i.e., left and right amygdala, left and right ventral striatum).

Aim 1. To examine cross-sectional neural correlates of irritability at baseline ($n = 176$, ages 4–8 at baseline), we specified a model with two between-subjects factors (irritability and age, both measured dimensionally) in relation to whole-brain connectivity for each seed. This model allowed us to examine both age-dependent (Irritability x Age interaction) and age-independent effects (Irritability main effect, adjusting for age).

Aim 2. Second, we examined the unique contribution of early irritability, above and beyond concurrent irritability, to predict change in brain connectivity over time. Similar to previous work that investigated brain development during this age (Geng et al., 2021; Riggins et al., 2016), we specified two sets of models, for the younger and older cohorts separately, to examine change in whole-brain connectivity, as follows: 1) irritability at time 1 predicting change in brain connectivity from time 1 to time 2, adjusting for irritability at time 2; 2) irritability at time 1 predicting the change in brain connectivity from time 1 to time 3, adjusting for irritability at time 3; 3) irritability at time 2 predicting the change in brain connectivity from time 2 to time 3, adjusting for irritability at time 3. Brain connectivity difference scores were calculated for each participant by subtracting the connectivity values at each voxel at the earlier time point from the respective values at the later time point (e.g., connectivity values at each voxel at time 1 subtracted from connectivity values at each voxel at time 2). We chose a whole-brain approach (vs. an ROI-to-ROI approach) in order to maximize our ability to detect associations across the entire brain, and because of the widespread effects that irritability can have on brain development. Moreover, while we considered examining interaction of irritability by time rather than difference scores, existing software does not fully support this time-varying analysis in a whole-brain manner. See Supplemental Table S1 for a breakdown of the sample sizes for each analysis in each cohort.

All analyses were corrected for multiple comparisons using a whole-brain corrected threshold of $p < .05$, with a height threshold of $p < .005$ resulting in an extent threshold of $k \geq 31$, calculated using AFNI's 3dClustsim with the mixed-model spatial autocorrelation function (-acf) and the NN1 2-sided option, per the most recent recommendations (Cox et al., 2017). 3dClustsim applied a group mask consisting of brain regions where 90% of participants have valid data. Additionally, we

applied a post-hoc Bonferroni correction to the significance values associated with the effects of interest in the clusters that emerged in our analyses. With four different seeds examined in Aim 1, effects were considered to pass multiple comparison correction if the significance value is lower than 0.05/4 = 0.0125. In the longitudinal analyses, Bonferroni correction accounted for the 24 parallel analyses that were conducted – that is, 0.05/24 = 0.002.

2.3.4. Additional analyses

We conducted additional analyses to investigate the potentially confounding role of sex, head motion, and non-irritable depression and anxiety symptoms on our results. To evaluate these factors in a targeted manner, connectivity values were extracted from significant clusters and averaged for each individual. The statistical models were then re-evaluated at the post-hoc level, after adding each of the potentially confounding variables, one at a time, to the model.

3. Results

Table 1 summarizes participant characteristics. Cross-sectionally, irritability had a $M = 0.81$ with a SD = 1.10 and a range= 0–5. There was an observable decline in irritability symptoms over time in both cohorts (i.e., irritability in younger cohort: time 1 *M (SD)* = 1.12 (1.32), time 2 *M (SD)* = 1.12 (1.15), time 3 *M (SD)* = 0.75 (1.30); irritability in older cohort: *M (SD)* = 0.86 (0.99), time 2 *M (SD)* = 0.80 (1.06), time 3 *M (SD)* = 0.76 (1.03)); however, these declines were not statistically significant.

Table 1
Demographic and clinical characteristics.

	Aim 1	Aim 2	
	N = 176	Younger Cohort (age 4 at baseline) n = 34	Older Cohort (age 6 at baseline) n = 29
Sex, % female	51.10%	47.10%	34.50%
Age (years)			
Mean (SD)	6.27 (1.50)	4.44 (0.25)	6.49 (0.30)
Range	4.02–8.97	4.02–4.99	5.94–6.98
Irritability (baseline)			
Mean (SD)	0.81 (1.10)	1.12 (1.32)	0.86 (0.99)
Range	0–5	0–5	0–3
n	176	34	29
Irritability (time 2)			
Mean (SD)		1.12 (1.15)	0.80 (1.06)
Range		0–3	0–3
n		31	26
Irritability (time 3)			
Mean (SD)		0.75 (1.30)	0.76 (1.03)
Range		0–6	0–4
n		32	26
Anxiety (baseline)			
Mean (SD)	2 (2.30)	3 (1.91)	2 (2.07)
Range	0–9	0–7	0–8
Depression (baseline)			
Mean (SD)	1.45 (1.69)	2 (1.91)	1.04 (1.29)
Range	0–8	0–8	0–5
Race & Hispanic Ethnicity (%)			
White	77.3%	91.2%	86.2%
African American	22.2%	8.8%	20.7%
Asian	16.5%	14.7%	17.2%
American Indian or Alaskan Native	2.3%	2.9%	3.4%
Native Hawaiian of Pacific Islander	0.6%	0.0%	0.0%
Did Not Disclose Race	2.8%	5.9%	0.0%
Hispanic Ethnicity	13.1%	5.9%	10.3%

Note: Continuous variables are displayed as M (SD); categorical variables are displayed as N (%); SD = Standard Deviation; Summation of race categories does not equal 100% (reported as valid percent), as families could identify as more than one race; Irritability, Anxiety, and Depression scores were derived from the parent-reported CBCL.

3.1. Neuroimaging results

All significant clusters of interest that resulted from whole-brain corrected connectivity analyses (left and right amygdala, left and right ventral striatum) are listed in Table 2. Additionally, the post-hoc significance values associated with the effects of interest were all < 0.001 and, therefore, all met the Bonferroni corrected threshold in both Aim 1 and Aim 2.

Aim 1: Cross-sectional evaluation of age-independent and age-dependent neural correlates of irritability.

Greater levels of baseline irritability, adjusting for age, were associated with increased left amygdala connectivity with the right posterior cingulate gyrus, representing an age-independent effect (partial eta squared: 0.094; Fig. 1). No significant clusters emerged in analyses examining age-dependent effects of irritability on amygdala or ventral striatum connectivity (i.e., Irritability x Age interaction).

Aim 2: Early irritability as a predictor of change in brain connectivity.

Early childhood irritability predicted decreases in connectivity as children aged. Specifically, higher parent-reported irritability at age 4, controlling for irritability at age 5, predicted decreases in left amygdala connectivity with the precentral gyrus (partial eta squared: 0.493) and right amygdala connectivity with medial frontal gyrus (partial eta squared: 0.409) from age 4 to 5 (Fig. 2 A). Similarly, greater levels of irritability at age 4, controlling for irritability at age 6, predicted decreases in right amygdala-left lingual gyrus connectivity from age 4 to 6 (partial eta squared: 0.503; Fig. 2 C). Finally, higher irritability at age 5,

Table 2
Significant clusters of interest resulting from whole brain connectivity analyses.

Aim 1							
Left Amygdala Connectivity							
Irritability							
k	**$F_{1,172}$**	**x**	**y**	**z**	**BA**	**Region**	**Partial eta squared**
38	14.2	4.5	-46.5	32.5	31	Posterior Cingulate	0.094
Aim 2 (Younger cohort: Change in connectivity from age 4 to 5)							
Left Amygdala Connectivity							
Irritability Time 1							
k	**$F_{1,31}$**	**x**	**y**	**z**	**BA**	**Region**	**Partial eta squared**
36	20.2	25.5	-19.5	62.5	4, 3	Right Precentral Gyrus	0.493
Right Amygdala Connectivity							
Irritability Time 1							
37	17.7	1.5	-13.5	47.5	6, 31	Medial Frontal Gyrus	0.409
Aim 2 (Younger cohort: Change in connectivity from age 4 to 6)							
Right Amygdala Connectivity							
Irritability Time 1							
k	**$F_{1,29}$**	**x**	**y**	**z**	**BA**	**Region**	**Partial eta squared**
37	34.6	-19.5	-94.5	-12.5	17, 18	Left Lingual Gyrus	0.503
Aim 2 (Younger cohort: Change in connectivity from age 5 to 6)							
Left Ventral Striatum Connectivity							
Irritability Time 2							
k	**$F_{1,28}$**	**x**	**y**	**z**	**BA**	**Region**	**Partial eta squared**
44	20.9	-7.5	16.5	2.5	-	Left Caudate	0.574
35	20.8	-4.5	-52.5	23.5	30, 23	Left Posterior Cingulate	0.394

Note: BA=Brodmann Area; clusters are presented in Figs. 1 and 2.

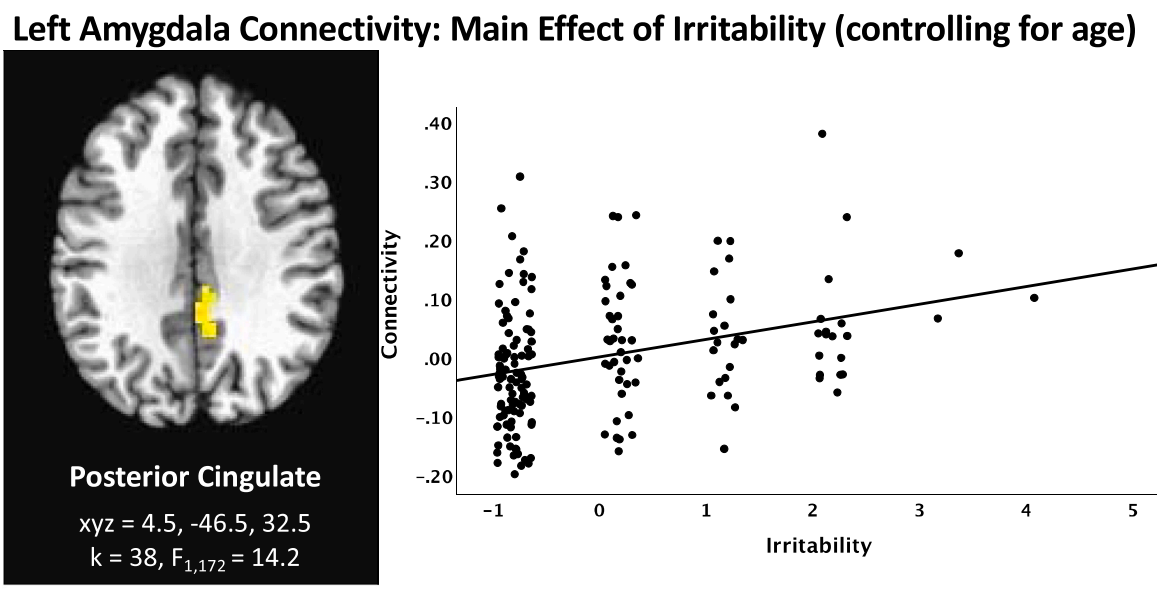

Fig. 1. Whole-brain Connectivity Analyses. *Main Effect of Irritability (controlling for age)*. Left amygdala connectivity with posterior cingulate. Scatterplot represents the relationship between whole-brain connectivity and irritability at baseline (N = 176). Brain regions represent axial sections (left=left) with threshold set at whole-brain FDR-corrected $p < .05$. The scatterplot is displayed for illustrative purposes to depict the direction of the association.

controlling for irritability at age 6, predicted decreases in left ventral striatum with the left caudate (partial eta squared: 0.574) and left posterior cingulate (partial eta squared: 0.394) from age 5 to 6 (Fig. 2B). All of these results were in the younger cohort (4-year-olds at baseline); no significant clusters emerged for the older cohort (6-year-olds at baseline).

See Supplemental Table S2 for all contrasts from the models, including the main effect of age.

3.2. Additional analyses

All clusters remained significant after adjusting for non-irritable depression, anxiety, age, sex, and head motion. Post-hoc sensitivity analyses that excluded children (aim 1 n = 3; aim 2 n = 1) with the highest levels of irritability (i.e., CBCL scores of 4 or 5) from each model did not change results.

4. Discussion

The goal of this study was to investigate the relationship between irritability and amygdala and ventral striatum connectivity to the whole-brain at rest during a key transition period from preschool- to school-age. To our knowledge, this is the first irritability-related study to have multiple functional neuroimaging timepoints in a sample this young (i.e., ages 4–8 years). This developmental period is important to investigate with respect to irritability and intrinsic functional connectivity, as irritability normatively declines over this period, and children who fail to follow this normative decline in their irritability are at higher risk for later problems (Copeland et al., 2015; Dougherty et al., 2015). As such, it is important to understand how deviations from normative irritability levels are reflected on a neural level, in order to further leverage findings to inform the development of novel, mechanistic treatments. That is, better understanding how irritability affects longitudinal connectivity changes may allow us to intervene early to promote adaptive brain maturation through mechanistic, behavioral and, potentially, pharmaceutical, or other novel interventions that modify brain connectivity directly. Although age dependent associations between irritability and connectivity did not emerge cross-sectionally in this sample of children aged 4–8 years, we observed significant longitudinal associations such that earlier irritability predicted changes in intrinsic connectivity between ages 4 and 6 years. These neuroimaging findings underscore the importance of longitudinal research to detect changes and the need for more studies that examine how irritability affects brain development – and how aberrant connectivity may be linked to poorer outcomes in the future. Moreover, if a link between aberrant connectivity changes and poorer longer-term outcomes is found, screening for elevated irritability early on could help intervene early and possibly prevent maladaptive further brain development through targeted interventions. Whereas the conventional wisdom was that misbehavior is too prevalent in early life to distinguish normative vs. abnormal irritability (Benarous et al., 2021) (thus leading to the age 6 minimum for the chronic severe irritability diagnosis in DSM-5, disruptive mood dysregulation disorder; APA, 2013), our findings with early neurodevelopmental changes (as young as 4–6 years) underscore the burgeoning literature showing that, in fact, early irritability can be linked with significant impairment (Wiggins et al., 2021, 2018). Our findings set the stage for additional research aimed at investigating irritability neurodevelopmental trajectories in even younger age cohorts (e.g., at the transition to toddlerhood), given the importance of interrupting the clinical cascade at the earliest possible point (Wakschlag et al., 2019).

Although results from the cross-sectional analyses (Aim 1) did not reveal age-dependent effects, we found a significant relationship between amygdala connectivity and level of irritability regardless of age. Our results revealed that increased irritability was related to increased left amygdala connectivity with the posterior cingulate. These findings are complementary to previous resting-state work investigating irritability in childhood. Both Stoddard et al. (2015) and the present study found evidence that irritability in childhood is related to altered intrinsic amygdala connectivity; however, Stoddard et al. (2015) found irritability-related amygdala connectivity changes in prefrontal regions whereas the present study found changes in the posterior region (cross-sectionally). Given the present study's focus on the amygdala and ventral striatum, these findings are also broadly aligned with previous task-based fMRI work that has demonstrated associations between elevated irritability in childhood and aberrancies in amygdala activation specifically (i.e., the amygdala; Dougherty et al., 2018) and amygdala and ventral striatum connectivity more generally (Dougherty et al., 2018; Wiggins et al., 2016). Despite differences in fMRI acquisition approaches and analytic strategies across these studies, and given the

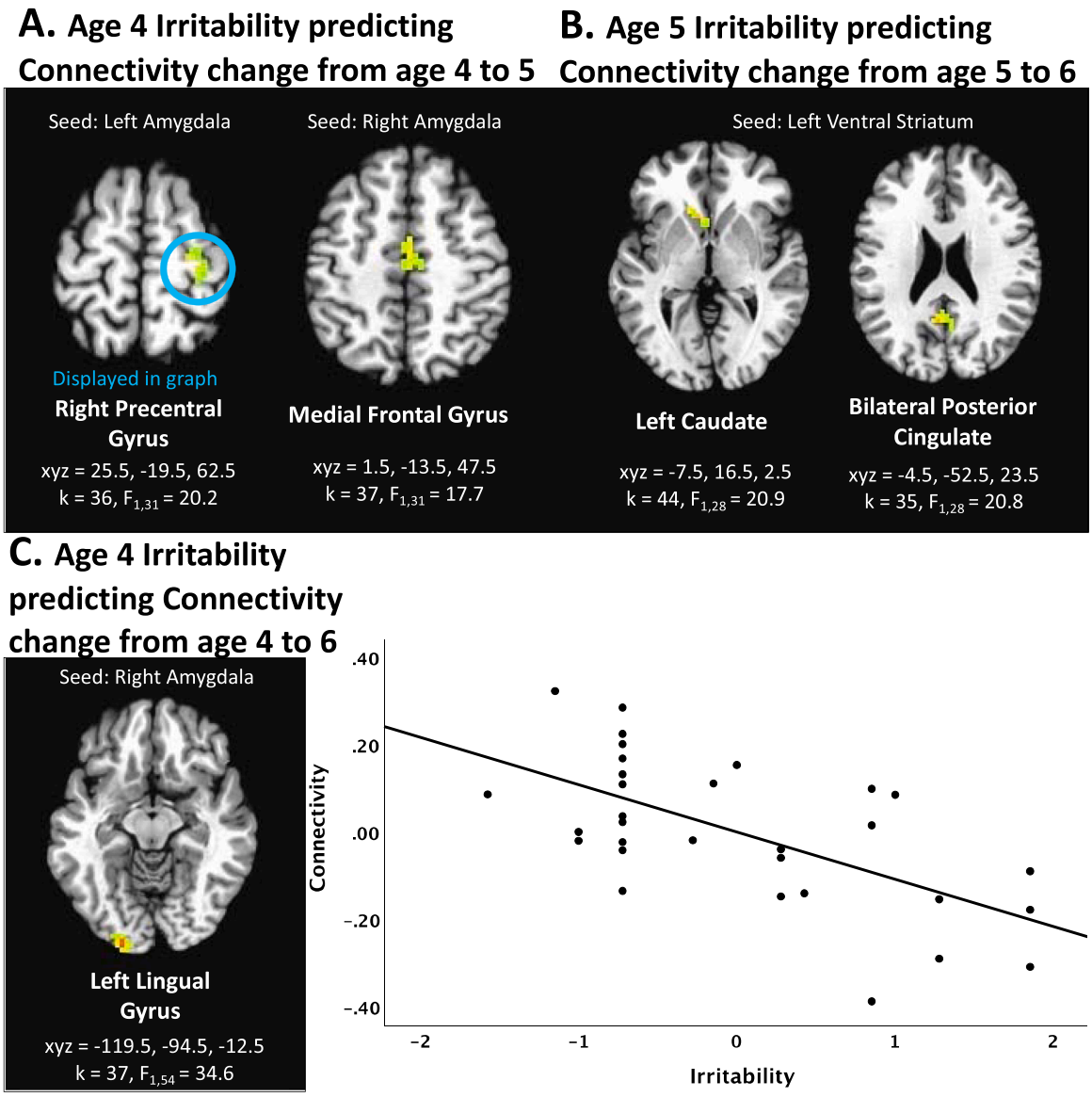

Fig. 2. Whole-brain Connectivity Analyses (younger cohort). A) *Age 4 Irritability predicting connectivity change from age 4 to 5* (n = 34). Left amygdala connectivity with right precentral gyrus and right amygdala connectivity to middle frontal gyrus. B) *Age 5 Irritability predicting connectivity change from age 5 to 6* (n = 31). Left ventral striatum connectivity with left caudate and bilateral posterior cingulate. C) *Age 4 Irritability predicting connectivity change from age 4 to 6* (n = 32). Right amygdala connectivity with left lingual gyrus. Graph represents relationship between irritability and change in connectivity (adjusting for irritability at a later timepoint) for left amygdala connectivity with the right precentral gyrus. Directionality of the predicted change in connectivity was similar across all significant clusters in the longitudinal analyses. Brain regions represent axial sections (left=left) with threshold set at whole-brain FDR-corrected $p < .05$. Graph is displayed for illustrative purposes to depict the direction of the association.

amygdala and ventral striatum's role in threat and reward processing respectively (e.g., Machado et al., 2009; Taswell et al., 2018), the present study provides further evidence that these processes may be implicated in irritability.

Results from our longitudinal analyses (Aim 2) yielded complementary results to our cross-sectional analyses and revealed some age-dependent effects. Overall, longitudinal analyses in the younger cohort revealed that higher irritability at age 4 predicted decreases in connectivity over time (controlling for irritability levels at later ages), whereas lower levels of age 4 irritability predicted increases in connectivity. These findings align with the interactive specialization approach to neural development proposed by Johnson (2000), whereby the normative increase in specialization that occurs with age is reflected in increased (i.e., "refined") connectivity (Battista et al., 2018; Johnson, 2000; Riley et al., 2018); we see this pattern in children with low irritability at baseline. By contrast, decreases in connectivity among children with elevated baseline irritability may reflect delayed specialization. It is also possible that because of increased specialization and neurodevelopmental maturity in middle and later childhood (Casey et al., 2000, 2005; Johnson, 2000) connectivity changes are more difficult to detect as children age which may help explain the null findings in the older cohort. Increased specialization along with potentially decreased variance in the older cohort may make the irritability-brain-age relationships harder to tease apart. However, given the preliminary nature of the present study, future work would benefit from focusing on groups with narrower age ranges in order to better tease apart age-related changes and differences in neural irritability development across childhood.

Finally, we found evidence for altered connectivity between key threat and reward regions (amygdala and ventral striatum) and posterior default network regions associated with irritability. Specifically, altered amygdala-PCC connectivity was found cross-sectionally,

whereas altered ventral striatum-PCC connectivity was found longitudinally. The default network is highly active at rest and is related to multiple social cognitive functions, including mentalizing/theory of mind, perspective taking, and understanding self vs. other, creating a narrative of the self, as well as mind-wandering/day-dreaming (Buckner et al., 2008; Fox et al., 2005). Given that the PCC is a major hub of the default mode network, while speculative, our preliminary findings suggest that social cognitive dysfunction, in addition to threat and reward, may be involved in irritability (as suggested by the amygdala/ventral striatum-PCC connectivity). This is consistent with prior behavioral and neural findings that children with irritability have difficulty labeling facial emotions (Guyer et al., 2007; Rappaport et al., 2018; Rich et al., 2008; Wiggins et al., 2016). Our findings moreover suggest that such social cognitive dysfunction may be linked to both reward *and* threat pathways of irritability, as altered connectivity of default network regions with both amygdala and ventral striatum were implicated in irritability. Further exploration of how social cognition, reward, and threat may interact to produce changes in irritability and, thus, neural network connectivity, is warranted.

Indeed, understanding the neural underpinnings of neurodevelopmental vulnerability markers, such as irritability, contributes to a growing science base that may provide the foundation for novel interventions to prevent the ensuing clinical cascade (Mittal and Wakschlag, 2017). Previous work has shown early irritability to be a robust predictor of psychopathology (Wiggins et al., 2021). The present study adds to this burgeoning area of research by revealing how early irritability also predicts changes in neural connectivity networks known to be related to threat and reward neural substrates that are often implicated in psychopathology (e.g., depression, anxiety, bipolar disorders). These findings further highlight the importance of early irritability as a screening target for early detection of future psychopathology.

5. Limitations

There are several limitations to the present study. First, although our longitudinal design establishes precedence in time, given the correlational nature of the study, causation cannot be inferred. Second, due to the moderate sample size of the longitudinal cohorts, we may miss small effects. However, this study builds the foundation for replication and extension in future, larger studies. Third, our community sample, with relatively fewer children with higher levels of irritability, limits our ability to generalize our results to those with very high, clinical levels of irritability. Follow-up studies using larger transdiagnostic clinical samples will be necessary in order to further elucidate these relationships. Fourth, the internal consistency of our irritability measure (i.e., CBCL) was slightly below desired thresholds (0.68 vs 0.70). As such, our preliminary analyses should be interpreted with caution, and follow-up studies should consider using a modified CBCL irritability scale, or other irritability scales (e.g., Multidimensional Assessment of Preschool Disruptive Behavior (MAP-DB), Affective Reactivity Index (ARI)). Finally, some evidence suggests that resting-state scans of less than 10 min in duration, such as the scans used in the present study, have lower reliability than longer or multi-session scans (Gordon et al., 2017; Noble et al., 2017). Follow-up studies are needed to validate the present findings.

6. Conclusion

The present study provides a cross-sectional and longitudinal perspective on the neural processes linked to irritability throughout early childhood. Our findings demonstrate the dynamic interaction in irritability and its neural mechanisms across a crucial transition from preschool- to school-age, and underscore the importance of investigating pathophysiological models of pediatric irritability and earlier, and more frequent, screening of irritability throughout childhood. Future work may wish to build on our findings and further examine neural and behavioral trajectories in even smaller age ranges in order to identify more specific potential targets (e.g., biomarkers) for intervention so that such trajectories may be changed for the better.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data statement

The datasets for this study will not be made publicly available because the data are undergoing secondary analyses in preparation for additional publications.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.dcn.2023.101206.

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