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Associations of Irritability With Functional Connectivity of Amygdala and Nucleus Accumbens in Adolescents and Young Adults With ADHD

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Abstract

Objective: Irritability is a common characteristic in ADHD. We examined whether dysfunction in neural connections supporting threat and reward processing was related to irritability in adolescents and young adults with ADHD. **Method:** We used resting-state fMRI to assess connectivity of amygdala and nucleus accumbens seeds in those with ADHD ($n = 34$) and an age- and gender-matched typically-developing comparison group ($n = 34$). **Results:** In those with ADHD, irritability was associated with atypical functional connectivity of both seed regions. Amygdala seeds showed greater connectivity with right inferior frontal gyrus and caudate/putamen, and less connectivity with precuneus. Nucleus accumbens seeds showed altered connectivity with middle temporal gyrus and precuneus. **Conclusion:** The irritability-ADHD presentation is associated with atypical functional connectivity of reward and threat processing regions with cognitive control and emotion processing regions. These patterns provide novel evidence for irritability-associated neural underpinnings in adolescents and young adults with ADHD. The findings suggest cognitive and behavioral treatments that address response to reward, including omission of an expected reward and irritability, may be beneficial for ADHD. (*J. of Att. Dis.* 2022; 26(7) 1040-1050)

Keywords

functional connectivity, irritability, adolescence, ADHD, amygdala, nucleus accumbens

Introduction

Irritability—prone to anger and agitation—is common in individuals with ADHD, affecting between 25% and 70% of youth with the disorder (Geller et al., 2002; Shaw et al., 2014). In adolescents with ADHD, irritability is associated with increased sleep problems, social difficulties, parental stress, and days missed from school (Mulraney et al., 2017) and alarmingly, related to a marked increase in risk for suicide completion (James et al., 2004), engaging in self-harming behaviors (Swanson et al., 2014), and substance abuse (Harty et al., 2017). However, despite the clinical importance of irritability combined with ADHD, relatively little is known about the underlying pathophysiology.

Alterations in threat- and reward-based processing neural circuits have been proposed to account for irritability. Specifically, altered function of a circuit comprising the prefrontal cortex (PFC), anterior cingulate cortex (ACC), striatum, and amygdala may give rise to irritability in

response to a frustrative non-reward, that is, a result of not attaining a goal (Brotman et al., 2017). In contrast, dysfunction in a circuit involving the PFC, amygdala, hypothalamus, and periaqueductal gray may propel irritability in response to a threat such as, for example, aggressive acts or

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criticism (Brotman et al., 2017). Previous studies suggest that emotional lability—a construct related to irritability—is associated with altered functional connectivity of the amygdala in those with ADHD (Hulvershorn et al., 2013; Yu et al., 2020). Neuroimaging of resting-state functional connectivity—that is, the temporal correlation of neural activity between brain regions during rest—is a common approach to assess altered communication among spatially remote brain regions in clinical populations (Fox & Greicius, 2010). Compared to previous research reporting atypical amygdala functional connectivity, less is known about connectivity in reward processing regions and their association with irritability despite ample evidence that alterations in striatal-reward regions are common in those with ADHD (Konrad & Eickhoff, 2010; Rubia, 2018; Samea et al., 2019). To address this gap in the literature, we examined both amygdala and nucleus accumbens (NAcc) connectivity to determine whether irritability in adolescents and young adults with ADHD is associated with atypical connectivity of these two regions that form part of these two networks, with other brain regions. Identifying such connections may provide new clues about what behaviors to intervene with depending on the regions with which the amygdala and NAcc demonstrate coordinated communication in relation to irritability.

We focused on the amygdala as a central region within the threat-based circuit and on the NAcc as a central region within the reward processing circuit. In children with ADHD, previous resting-state investigations suggest an association between emotional lability and increased functional connectivity between the amygdala and the rostral ACC as well as decreased functional connectivity with posterior insula/superior temporal gyrus (Hulvershorn et al., 2013). Longitudinally, among children with ADHD, an irritable subtype—characterized by increased negative emotionality and greater risk for subsequent comorbidities—exhibited reduced amygdala–insula functional connectivity (Karalunas et al., 2014). A more recent study also employing a seed-based approach reported an association between higher emotional lability and lower functional connectivity of a subregion of the right amygdala with the right dorsolateral PFC and bilateral inferior parietal lobes (Yu et al., 2020). The limited overlap in findings among these studies suggests that more attention is needed to understand the relation between irritability in ADHD and underlying threat circuitry function.

Given these preliminary findings, irritability in ADHD is likely to be associated with dysfunctional amygdala functional connectivity. However, common abnormalities in reward processing suggest that functional connectivity of striatal regions may also play a role in irritability in youth with ADHD, possibly contributing to aberrant behavioral response to frustrative non-rewards (Brotman et al., 2017). Compared to the general population, adolescents and adults

with ADHD show striatal hypo-responsiveness during reward anticipation (Plichta & Scheres, 2013). Additionally, resting-state functional connectivity between the left NAcc and the left orbitofrontal cortex correlated with symptoms of emotional lability in 7- to 12-year-old children diagnosed with ADHD (Posner et al., 2013). Behaviorally, children with ADHD prefer immediate, small rewards over larger, delayed rewards (Marco et al., 2009; Marx et al., 2021; Schweitzer & Sulzer-Azaroff, 1995), which has been linked to both NAcc-PFC functional connectivity and amygdala hyperactivity (Costa Dias et al., 2013; Plichta et al., 2009). Taken together, these studies suggest that aberrant functional connectivity in the reward network, and involving the NAcc specifically, may contribute to irritability symptoms in ADHD.

We examined functional connectivity of the amygdala and NAcc seeds and their relations to increased irritability symptoms in those with ADHD, compared to age- and gender-matched typically developing (TD) adolescents and young adults. Informed by prior research using resting-state functional connectivity to examine the neural basis of irritability and emotional lability in children and adults with ADHD (Hulvershorn et al., 2013; Karalunas et al., 2014; Yu et al., 2020), we hypothesized that higher irritability symptoms would be associated with altered resting-state connectivity of the amygdala and NAcc in adolescents and young adults with ADHD, compared to their TD peers. We predicted that functional connectivity with regions of the PFC would be particularly sensitive to differing levels of irritability but refrained from making specific predictions about the direction of connectivity.

Method

Participants

In the total ADHD sample, participants included 56 adolescents and young adults (aged 12–23 years) with a diagnosis of ADHD-Combined Presentation. Following exclusion criteria and sample-matching procedures detailed below, the final sample in the current study included 34 youth in the ADHD group and 34 youth in the TD group. We refer to the participants as “adolescents,” acknowledging that the age span includes young adults as well. Two licensed psychologists with extensive experience diagnosing ADHD (JFD, JBS) evaluated initial phone screening data to determine eligibility for the study. Participants meeting the phone screen criteria were invited to proceed to the next phase of the study, which included an in-depth, in-person psychological evaluation. Participants were evaluated according to the Diagnostic and Statistical Manual of Mental Disorders-IV-TR or 5th Edition (DSM 5, which was used upon its publication) criteria for ADHD and all other major psychiatric disorders (e.g., mood disorders, anxiety,

Table 1. Medication Information for the ADHD group.

	N
Number of subjects unmedicated	11
Number of subjects medicated	23
Atomoxetine	1
Methylphenidate hydrochloride extended release (Concerta)	5
Dextro-amphetamine (Adderall)	2
Dextro-amphetamine extended release (Adderall XR)	7
Lisdexamfetamine dimesylate (Vyvanse)	5
Methylphenidate	2
Dexmethylphenidate HCL extended release (Focalin XR)	1

obsessive-compulsive, trauma, psychosis, addiction, oppositional defiant, and conduct disorders). Diagnostic interviews included the participant and one of their parents/caregivers for adolescents, while adult participants could choose to have their parents, partner, or spouse rate their current behavior, depending upon who was most familiar with their current behavior (Diagnostic Interview Schedule for Child and Adolescents and Young Adult version; Shaffer et al., 2000). Parents also reported on symptoms using the Conners-3 Parent Rating Scale (CPRS-3) or the Conners' Adult ADHD Rating Scale (CAARS-O), Observer Form—Long Version (with parent ratings on the young adults) (Conners, 2008). Parents of young adults also completed the Barkley Adult ADHD Rating Scale—Retrospective Scale (Barkley, 2011) to establish the presence of significant ADHD behavior before the age of 12 years.

A licensed psychologist (JFD) reviewed all of the diagnostic information to determine final ADHD diagnosis and presence of other disorders based on the diagnostic interview and DSM Predominantly Inattentive and Predominantly Hyperactive/Impulsive Presentation Scales from the CPRS or CAARS. Conners-3 Teacher Rating Scales (CTRS) further informed diagnosis if there were contradictions between the interview and parent rating scale data. In complex cases (i.e., disagreement between CPRS, CTRS, and the clinical interview), further follow-up interviews were conducted by JFD, and JFD and JBS both reviewed all diagnostic information to make a final expert diagnosis determination.

Inclusion criteria included $IQ \geq 80$ and age between 12 and 23 years, with additional inclusion criteria for the ADHD group of meeting DSM-IV-TR or DSM-5 criteria for ADHD, Combined Presentation or Hyperactive/Impulsive Presentation. However, all participants in this study met criteria for the Combined Presentation and none for the Hyperactive/Impulsive Presentation. Exclusion criteria included: IQ score < 80 ; presence of a math or reading learning disability; a self- or parent-reported history of head trauma, neurological disorder, or major medical problem; prescribed psychoactive medication beyond ADHD medications (i.e., other than stimulants or atomoxetine);

presence of any other DSM-IV-TR or DSM-5 Axis I diagnosis besides ADHD, oppositional defiant disorder, or conduct disorder; a positive drug screen on the day of the imaging session; and MRI contra-indications. Of the 56 clinical participants, 22 (39%) were excluded due to excessive head motion (mean frame-wise displacement > 0.35) resulting in a final clinical sample of 34 adolescents with ADHD (22 male, 12 female). The 22 excluded participants did not differ significantly from the remaining 34 patients in their average IQ, inattentive symptoms, and irritability ratings or, in the distribution of gender, race, ethnicity, household income, and maternal education. The excluded participants were however on average younger ($t(54) = 3.134, p = .003$) and with higher hyperactive-impulsive symptoms ($t(53) = -2.657, p = .010$). Twenty-three of the ADHD participants were on prescription medication (see Table 1 for medication information) but withheld medication for 48 to 96 hours (i.e., at least five half-lives) prior to the MRI scan with their physician's approval. Thirty-four TD adolescents were matched to the ADHD group on sex, age, head motion (see Table 2). The same exclusion criteria applied to this control group with the addition of a score < 60 on the CPRS-3 or CAARS ADHD Total Scale. Table 2 shows average symptom scores and demographic information for each group. Informed written parental consent and child assent were obtained from all participants. The University of California, Davis Institutional Review Board approved the study.

Measures. *Conners' Parent Rating Scale—3* (Conners, 2008): The CPRS-3 contains 108-items that are rated on how frequently certain behaviors occur from 0 (never, seldom) to 3 (very often). The questionnaire has good internal reliability (Cronbach's α ranging from .75 to .94 for all scales), high test-retest reliability, and effective discriminatory power (Conners et al., 1998).

Conners' Adult ADHD Rating Scales (CAARS-O) (observer ratings): For participants aged 18 and over, ADHD symptoms were assessed by the CAARS-O. Internal consistency of the CAARS-O subscales ranges from 0.81 (Hyperactivity/Restlessness) to 0.89 (Problems With Self-Concept) (Conners et al., 1999).

For the purpose of the present study, a separate score for irritability was derived by summing scores on items 14, 48, 73, 81, 100 of the CPRS-3 and items 8, 19, 23, 61 of the CAARS-O. Internal consistency of the CPRS-3 and CAARS irritability items were 0.92 and 0.84 respectively. The items chosen from each questionnaire correspond to items on the Affective Reactivity Index (ARI) (Stringaris et al., 2012). To validate our irritability measure we correlated CPRS-3 and CAARS irritability scores with ARI scores in a subsample of participants that completed both questionnaires. Correlations were high: CPRS-3 ($n = 21$): $r = .96, p < .0001$; CAARS ($n = 12$): $r = .71, p = .01$.

Table 2. Demographic, Clinical, and MRI Head Motion Information for the ADHD and Control Groups.

	ADHD (n = 34)	TD (n = 34)	Statistic
Gender: Male/female	22/12	22/12	
Mean (SD) Age (years)	16.29 (2.68)	15.99 (2.85)	$t(66) = 0.46, p = n.s.$
Race: White/Black or African American/ Asian/Multiracial/other or unknown	25/1/0/7/1 (73.5%/2.9%/0%/20.6%/2.9%)	18/2/2/10/2 (52.9%/5.9%/5.9%/29.4%/5.9%)	$\chi^2(4, N = 68) = 4.34, p = n.s.$
Ethnicity: Not Hispanic/Hispanic/unknown	22/8/4 (64.7%/23.5%/11.8%)	24/10/0 (70.6%/29.4%/0%)	$\chi^2(2, N = 34) = 4.31, p = n.s.$
Maternal education: bachelor's degree or higher	28 (82.4%)	27 (79.4%)	$\chi^2(1, N = 68) = .10, p = n.s.$
Household income: above \$100k	19 (55.9%)	12 (35.3%)	$\chi^2(1, N = 68) = 2.62, p = n.s.$
Mean (SD) IQ	106.82 (11.56)	114.15 (10.11)	$t(66) = -2.78, p = .007$
Mean (SD) Conners' DSM inattention*	80.91 (10.37)	42.56 (5.10)	$t(48.08) = 19.35, p < .001$
Mean (SD) Conners' DSM hyperactive/ impulsive*	78.21 (12.19)	43.35 (4.71)	$t(42.64) = 15.55, p < .001$
Mean (SD) irritability	6.32 (3.90)	1.21 (1.68)	$t(44.9) = 7.03, p < .001$
Mean (SD) framewise displacement	0.19 (0.09)	0.17 (0.06)	$t(66) = 0.98, p = n.s.$
Mean (SD) relative motion (mm)	0.09 (0.04)	0.09 (0.03)	$t(66) = 0.94, p = n.s.$
Mean (SD) absolute motion (mm)	0.33 (0.23)	0.25 (0.17)	$t(66) = 1.60, p = n.s.$

*Mean score based on the *t*-scores for the CPRS' Parent Scores (participants 17 years and younger) and CAARS-O (participants 18 years and older).

Resting state MRI data acquisition: Imaging data were acquired on a Siemens 3.0 T TIM Trio MRI scanner. T2-weighted functional images were acquired with the following parameters: TR = 2,000 ms; TE = 25 ms; flip angle = 80°, 36 slices, matrix = 64 × 64; FOV = 220 mm; voxel size = 3.4 × 3.4 × 3.4 mm. The duration of the resting state scan was 6 minutes 4 seconds. The T1-weighted high-resolution anatomical image was acquired with the following parameters: TR = 1,900 ms; TE = 3.06 ms; flip angle = 8°; 160 slices; FOV = 256 mm; acquisition voxel size = 1.0 × 1.0 × 1.0 mm. Participants were instructed to look at a fixation point during the scan acquisition.

Functional connectivity analysis. All analyses including image preprocessing were carried out using the CONN toolbox v. 17.0 (<http://www.nitrc.org/projects/conn/>) (Whitfield-Gabrieli & Nieto-Castanon, 2012). T1 structural scans were segmented into gray matter, white matter, and cerebrospinal fluid and then normalized to the Montreal Neurological Institute (MNI) template. Preprocessing of functional images included slice timing correction, spatial coregistration of functional data to each participant's structural scan, spatial normalization to MNI space, and spatial smoothing using a 6 mm full-width-at-half-maximum Gaussian kernel. Prior to smoothing, we identified outlier volumes across subjects in acquisitions with a framewise displacement above 0.9 mm or global BOLD signal changes above 5 SD using artifact removal toolbox (ART) (https://www.nitrc.org/projects/artifact_detect/). For each subject, outlier volumes, head-motion (six-parameters of translation and rotation), and other spurious sources of noise (e.g., signal from white matter and cerebrospinal fluid) were regressed out using the aCompCor method (Behzadi et al., 2007). Then, temporal high-pass filtering (0.008–0.09 Hz) was applied to the residual BOLD time course to exclude remaining physiological noise (e.g., respiratory effects).

Seed regions were defined using the default ROIs within CONN based on the Harvard-Oxford Subcortical Atlas, left and right amygdala as well as left and right NAcc. First-level correlation maps were produced by extracting the denoised BOLD time course from each seed and computing Pearson's correlation coefficients between that time course and the time courses of all other voxels in the brain. Correlation coefficients were Fisher-transformed into *Z* scores, which increases normality and allows for improved second-level General Linear Model analyses. We adjusted the cluster significant threshold for the four seed regions to an FDR cluster-corrected threshold of $p < .0125$. Unpaired *t*-tests were performed to assess between-group differences in seed-to-voxel functional connectivity. As the groups were matched on sex, age, and head motion, we did not include these variables as covariates in our initial analysis. To ensure effects were due to irritability symptoms above and beyond hyperactive-impulsive symptoms as suggested previously (Hulvershorn et al., 2013) in a follow-up analysis we controlled for hyperactive-impulsive symptoms. We also assessed separately if results would hold if we controlled for differences in full-scale IQ.

Results

Demographic and clinical information for the sample is provided in Table 2. The groups were closely matched on age and sex and no significant differences were observed for maternal education level, household income, race, and ethnicity. As expected, the ADHD group scored significantly lower on full-scale IQ (though still in the normal range), and significantly higher on core ADHD symptom measures of inattention and impulsivity/hyperactivity and on irritability (see Table 2).

Amygdala seeds: A group × irritability interaction effect was found for functional connectivity between the left

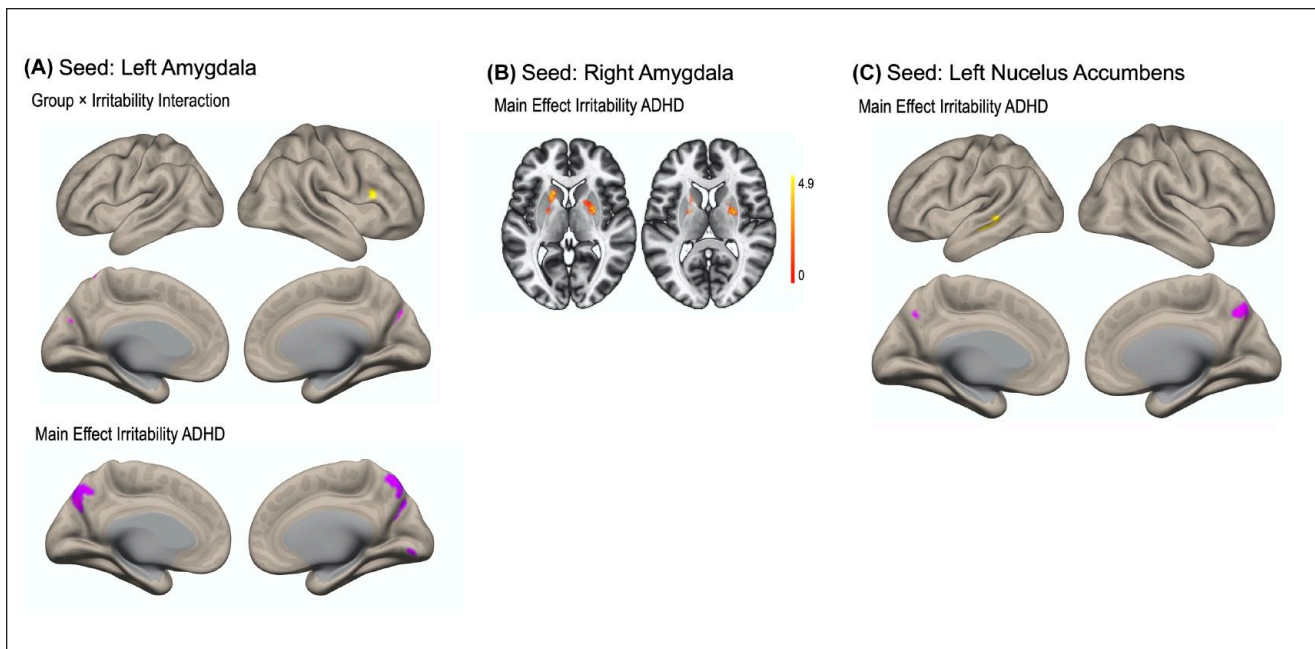


Figure 1. Resting-state functional connectivity maps with seeds in the left (A) and right (B) amygdala and left nucleus accumbens (C). (A) Irritability in the ADHD group was positively associated (yellow) with functional connections between the left amygdala and right inferior frontal gyrus and negatively (purple) with connectivity between the left amygdala and bilateral precuneus compared to the typically developing control group. (B) Irritability levels in the ADHD group were positively associated with functional connectivity between the right amygdala and bilateral putamen/caudate. (C) A main effect of irritability in the ADHD group revealed stronger connectivity between the left NAcc and a region in the left posterior middle temporal gyrus and weaker connectivity between the left NAcc and the precuneus.

amygdala and right inferior frontal gyrus and between the left amygdala and bilateral precuneus/cuneus (Figure 1, Table 3). Irritability symptoms were more positively associated with functional connectivity between the left amygdala and the right inferior frontal gyrus in the ADHD group compared to the TD group. For functional connectivity between the left amygdala and the bilateral precuneus/cuneus, irritability was more negatively associated in the ADHD compared to the TD group. This interaction was not observed for the right amygdala. Simple main effects of irritability in the ADHD group showed that higher irritability was associated with higher functional connectivity between the left amygdala and bilateral putamen/caudate and lower functional connectivity of the left amygdala with the precuneus and lingual gyrus. This simple main effect of irritability and functional connectivity with the putamen/caudate was also observed for the right amygdala. No simple main effect of irritability was observed in the TD group. Both the interaction and the simple main effects of irritability remained significant when controlling for hyperactive-impulsive symptoms. The group \times irritability interaction for the left amygdala also remained significant when covarying for IQ differences, suggesting that neither IQ nor hyperactive-impulsive symptoms were related to the observed associations with irritability.

Nucleus Accumbens seeds: No significant group \times irritability interaction effect for either the left or the right NAcc was found. A main effect of irritability in the ADHD group, however, showed that higher irritability was associated with greater functional connectivity between the left NAcc and a region in the left posterior middle temporal gyrus, and lower functional connectivity between the left NAcc and a cluster in the precuneus (Figure 1, Table 3). A trend for greater functional connectivity between the right NAcc and the left posterior middle temporal gyrus with higher levels of irritability was also observed but did not survive correction for multiple comparisons ($p = .025$). When statistically adjusting for symptoms of hyperactivity/impulsivity, the simple main effects of irritability observed for the left NAcc no longer survived the threshold for multiple comparisons ($p = .028$).

Discussion

Given poor outcomes for individuals with ADHD and high levels of irritability, we aimed to identify neural markers of irritability in adolescents with ADHD and contrast these to those within typically developing adolescents. We focused on two regions, the amygdala and the nucleus accumbens, to examine circuits that support reward and threat

Table 3. The Four Seed Regions (Left and Right Amygdala, Left and Right Nucleus Accumbens) and Significant Target Regions Associated with Irritability.

	Coordinates			Cluster size (k)	Beta	T	p
	x	y	z				
Seed: left amygdala							
Group × Irritability interaction							
(+) right IFG	+54	+16	+24	137	.08	4.85	.005
(-) precuneus/cuneal cortex	+22	-70	+32	136	-.08	-4.18	.005
(-) precuneus	-4	-60	+62	102	-.07	-4.23	.012
Main effect irritability: ADHD							
(-) precuneus	-14	-68	+38	1,310	-.03	-6.10	<.001
(-) lingual gyrus	+04	-82	-08	120	-.03	-4.02	.009
(+) left caudate/putamen	-18	+10	+04	144	.03	4.49	.005
Main effect irritability: TD							n.s.
Seed: right amygdala							
Group × Irritability interaction							n.s.
Main effect irritability: ADHD							
(+) bilateral putamen/caudate	-16	+16	+02	293	.03	4.68	.002
(+) right putamen/caudate	+26	-04	+10	262	.03	4.46	.003
Main effect irritability: TD							n.s.
Seed: left nucleus accumbens							
Group × Irritability interaction							n.s.
Main effect irritability: ADHD							
(-) precuneus	+10	-64	+40	163	-.03	-4.53	.002
(+) left pMTG	-52	-38	-04	126	.03	4.52	.004
Main effect irritability: TD							n.s.
Seed: right nucleus accumbens							
Group × Irritability interaction							n.s.
Main effect irritability: ADHD							
(+) left pMTG	-52	-40	-06	119	.02	4.42	.025
Main effect irritability: TD							n.s.

Note. All results are $p < .0125$ (FDR-corrected). (+) = indicates a positive association; (-) = indicates a negative association; IFG = inferior frontal gyrus; pMTG = posterior middle temporal gyrus.

behaviors. Crucially, we observed an association between irritability symptoms and functional connectivity between the amygdala and inferior frontal and posterior midline regions with varying irritability symptoms in the ADHD but not the TD group. In addition to the group differences, irritability symptoms in the ADHD group were also associated with greater functional connectivity between the amygdala and the caudate/putamen as well as between the left NAcc and a posterior temporal region. The results support altered functional connectivity of both threat and reward circuits, when ADHD is accompanied by irritability, extending to other key regions involved in cognitive control and emotion processing.

The observed association between irritability and functional connectivity between the left amygdala and the right IFG was significantly more positive in the ADHD group compared to the TD group suggesting a diminished ability for cognitive control, specifically inhibition and emotion regulation typically attributed to the IFG (Aron & Poldrack, 2005). Right IFG and amygdala show strong positive functional connectivity during task-based emotion paradigms (Kerestes et al., 2017) and become negatively connected during successful regulation of negative emotions (Ochsner

et al., 2012). As the observed positive association between irritability and IFG-amygdala functional connectivity remained even after controlling for hyperactive-impulsive symptoms, the results confirm previously reported associations with less efficient emotion regulation mechanisms in irritable youth (Leibenluft, 2017).

Compared to the TD group, irritability was negatively associated with functional connectivity between the left amygdala and posterior midline regions within the precuneus in the ADHD group. Amygdala-precuneus connections support successful emotion regulation by directing attention away from affective information (Ferri et al., 2016; Roy et al., 2009; Zhang & Li, 2012). Reduced functional connectivity therefore may increase irritability by preventing an attentional shift away from emotional stimuli (Ferri et al., 2016). Such altered or reduced connectivity between these two regions has been reported in several other psychopathologies known for high levels of irritability including children diagnosed with bipolar disorder (Rich et al., 2008; Stoddard et al., 2015), adolescents with depression (Cullen et al., 2014), adults with childhood maltreatment (van der Werff et al., 2013), post-traumatic stress disorder (Nicholson et al., 2015), and schizophrenia (Mukherjee et al., 2012).

Group by irritability interactions were only observed for the left but not right amygdala and with connectivity to right but not left IFG. The left amygdala has been shown to respond more consistently to negative emotions during task fMRI studies using emotion paradigms (Wager et al., 2008) and the right IFG plays a more dominant role in regulating emotions and during inhibitory control compared to its left counterpart. Even though we did not formally test laterality differences, atypical asymmetry in brain structure and function is a common observation in ADHD (Langleben et al., 2001; Shaw et al., 2009; Silk et al., 2016) and has also been implicated in the neurobiology of irritability (Althoff et al., 2017; Chaarani et al., 2020); as such it is likely, that left and right fronto-limbic and fronto-striatal connections differentially contribute to the pathophysiology of irritability in ADHD.

In the ADHD group, heightened irritability was associated with increased amygdala-striatal functional connectivity, suggesting associations between irritability and both altered reward processing and arousal (Beauchaine & Tackett, 2020; Brotman et al., 2017). Similarly, the left NAcc showed greater functional connectivity with a region in the left posterior middle temporal gyrus with increasing irritability in the patient group. The stronger functional connectivity between the two regions may thus hint at more rigid reward expectancies (Badre & Wagner, 2007) that may result in pathological temper outbursts or reactive aggression when reward expectancies are not met (Brotman et al., 2017). Given that there were no significant group differences for these associations these main effects should be interpreted cautiously. It is possible that the low variability of the irritability ratings in the TD group contributed to the lack of significant group differences. It would be valuable to compare the ADHD group to another clinical group to determine whether the main effects observed here are specific to ADHD. Additionally, a dimensional symptom-based approach independent of diagnostic category as proposed by the RDoC framework (Cuthbert & Insel, 2013) may provide complementary information on the neural underpinnings of irritability.

Our results differ from those reported by Hulvershorn et al. (2013), who found a positive association between emotional lability and left amygdala-medial PFC functional connectivity. Age differences across samples or measurement of irritability as compared to emotional lability may be relevant. Our findings also differ to some extent from those reported by Yu et al. (2020) who found that emotional lability was correlated positively with connectivity of the right (superficial) amygdala and dIPFC as well as inferior parietal regions. These authors, however, restricted their analysis to regions that initially showed significant between-group differences during a task. Significantly, comparable to our results, they found that the ADHD group exhibited weaker connectivity between the amygdala and the precuneus compared to controls.

Our findings should be interpreted in light of several limitations. First, although we used a well-validated clinical questionnaire, the instrument was not specifically developed to measure irritability and may have missed important aspects of the irritability phenotype (Vidal-Ribas et al., 2016). Second, our study is limited to a cross-sectional examination of irritability and functional connectivity. Given the long-term clinical implications of heightened irritability, it is important to examine neural markers of improvement or worsening of irritability-related impairments longitudinally. Third, our final sample size was diminished considerably after losing 39% of the clinical sample due to excessive head motion. Even though heightened head motion is common in participants with ADHD (Kong et al., 2014; Satterthwaite et al., 2012) the reduced sample size limits the generalizability of our results especially to younger ADHD participants and those with higher hyperactive-impulsive symptoms. Fourth, parental education and income, along with participant IQ, were relatively high, potentially also reducing generalizability. Thus, follow-up studies will need to recruit participants with more varied incomes and educational levels that reflect the general population. Lastly, differences in developmental stage or brain maturation may account for some of the results observed here given the wide age-range of our participants. Future studies may separately utilize irritability ratings, age, and individual brain maturation indices (Cao et al., 2015; Dosenbach et al., 2010; Truelove-Hill et al., 2020) to examine developmental and maturational effects on irritability in those diagnosed with ADHD and typically developing youth.

Our sample was carefully phenotyped clinically, and the results present important information on the neural correlates of irritability in adolescents, who are most representative of adolescents with the ADHD, Combined Presentation. We recruited participants with evidence of significant impulsivity and therefore, meet criteria for the Combined Presentation, and excluded volunteers with the Inattentive ADHD Presentation, because of a need in the field to characterize the relation between behavioral symptoms of impulsivity and associated neural functioning. Furthermore, there is evidence of functional connectivity differences between the Inattentive and Combined Presentations of ADHD (Fair et al., 2012) and thus recruiting from Inattentive ADHD populations may have obscured some potential findings.

Taken together, we revealed alterations in functional connectivity of the amygdala and the NAcc in association with heightened irritability in ADHD. Anomalies with connections to frontal, temporal, and posterior midline regions may give rise to not only increased impulsivity and difficulties in attention but also to heightened irritability. These observed associations between irritability and functional connectivity of NAcc and amygdala suggest treatments that address response to reward, primarily omission of an

expected reward and irritability may be beneficial for those with ADHD. This may include training to increase inhibitory and cognitive control or reduction in the effect of stimuli eliciting irritability, including cognitive or behavioral training such as exposure therapy (Kircanski et al., 2019; Linke et al., 2020), perhaps meditation techniques, or pharmacological approaches that affect how one responds to cues signaling reward loss, absence of an expected reward, and other situations associated with irritability.

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Declaration of Conflicting Interests

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