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Abnormal Amygdala Functional Connectivity Associated With Emotional Lability in Children With Attention-Deficit/ Hyperactivity Disorder

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Abstract

Objective—A substantial proportion of children with attention-deficit/hyperactivity disorder (ADHD) also display emotion regulation deficits manifesting as chronic irritability, severe temper outbursts, and aggression. The amygdala is implicated in emotion regulation, but its connectivity and relation to emotion regulation in ADHD has yet to be explored. The purpose of this study was to examine the relationship between intrinsic functional connectivity (iFC) of amygdala circuits and emotion regulation deficits in youth with ADHD.

Method—Bilateral amygdala iFC was examined using functional magnetic resonance imaging in 63 children with ADHD, aged 6 to 13 years. First, we examined the relationship between amygdala IFC and parent ratings of emotional lability (EL) in children with ADHD. Second, we compared amygdala iFC across subgroups of children with ADHD and high EL (n = 18), ADHD and low EL (n = 20), and typically developing children (TDC), all with low EL (n = 19).

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Results—Higher EL ratings were associated with greater positive iFC between the amygdala and rostral anterior cingulate cortex in youth with ADHD. EL scores were also negatively associated with iFC between bilateral amygdala and posterior insula/superior temporal gyrus. Patterns of amygdala-cortical iFC in ADHD participants with low EL were not different from the comparison group, and the effect sizes for these comparisons were smaller than those for the trend-level differences observed between the high-EL and TDC groups.

Conclusions—In children with ADHD and a range of EL, deficits in emotion regulation were associated with altered amygdala–cortical iFC. When comparing groups that differed on ADHD status but not EL, differences in amygdala iFC were small and nonsignificant, highlighting the specificity of this finding to emotional deficits, independent of other ADHD symptoms.

Keywords

attention-deficit/hyperactivity disorder; amygdala; emotional lability; functional magnetic resonance imaging (fMRI)

Although attention-deficit/hyperactivity disorder (ADHD) is diagnosed solely on the basis of deficits in attention, hyper-activity, and impulsivity, clinicians and parents have long observed that difficulties with emotion self-regulation represent key associated features.[1–3] A substantial proportion of children with ADHD exhibit frequent temper outbursts or "rage attacks," low frustration tolerance, and chronic irritability,[4,5] which carry different labels across research groups (e.g., emotional impulsivity,[6] emotional lability,[7] deficient emotional self-regulation,[8,9] negative emotionality,[10] or emotional dysregulation[11–13]). Although these behaviors occur in a number of psychiatric conditions,[14] a substantial proportion of children with ADHD exhibit difficulties regulating negative affect.[5,7,11,15,16] In 1 sample of 358 children, nearly half of those with ADHD exhibited significantly impairing levels of parent-rated emotional lability.[15] Conversely, in a sample of 5- to 9-year-olds recruited solely for concerns regarding severe tantrums, 75% were diagnosed with ADHD.[17] Such childhood deficits in emotion regulation appear to persist and predict later-life difficulties.[6] Specifically, 1 longitudinal study found that emotional impulsivity uniquely predicted impairment in 7 of 10 major adult life domains in children with ADHD followed into adulthood.[6] Furthermore, recent work supports the notion of a familial subtype of ADHD that is particularly characterized by emotion dysregulation.[8]

Current neurobiological models of ADHD suggest deficits in regulatory processes ascribed to brain areas within prefrontal cortex (PFC) and spanning network nodes throughout sensory and limbic cortex as well as striatal and cerebellar regions.[18–20] Such defects in prefrontal regulation have been hypothesized to account for the range of behavioral, cognitive, and emotional symptoms of ADHD.[21] This theory is supported by evidence of a thinner cortex in children with ADHD, most prominently in the medial and superior prefrontal and precentral regions involved in cognitive and emotional control.[22] Still, most neuroimaging studies have focused on the association between prefrontal control mechanisms and non-affective aspects of ADHD, such as deficits in working memory,[23] attention,[24,25] cognitive control,[26] and response inhibition.[27] By contrast, relatively little is known about emotion-related neural mechanisms in ADHD, especially early in development.

The amygdala is essential to the processing and regulation of emotional information and has received considerable experimental attention, both in animal and in human neuroimaging studies. Studies of individuals with ADHD are limited, although they do suggest alteration in amygdala structure and function. For example, children[28] and adults[29] with ADHD show behavioral deficits in specific functions typically associated with the amygdala, such as facial and contextual emotion processing. Structural neuro-imaging studies provide evidence

of ADHD-related differences in amygdala morphometry,[30] whereas functional studies in children with ADHD using negative emotional stimuli (i.e., fearful, anxious, angry faces) yield mixed results, with studies demonstrating amygdala hyper-activation,[31–33] hypoactivation,[34,35] or no differences[31,36] relative to healthy comparisons. A recent study found that children characterized as having severe mood dysregulation (SMD), a syndrome with particularly pronounced emotion regulation deficits and high rates of comorbid ADHD, exhibit hypoactivation of the left amygdala in response to neutral faces, relative to control and ADHD groups.[32] Of note, 83% of the SMD group were diagnosed with ADHD, which suggests that observed differences in amygdala response were related specifically to emotion dysregulation. A recent study of effective connectivity during a task probing negative emotions showed greater connectivity between amygdala and lateral PFC in unmedicated adolescents with ADHD compared to healthy comparisons, suggesting disruption of amygdala-based circuits.[37] Notably, stimulants normalized this connectivity. Thus, although evidence for ADHD-related disruptions in amygdala function and functional connections with PFC is building, the relationship with specific symptoms of emotion dysregulation has received little attention.

Intrinsic, or resting state, functional connectivity (iFC), a measure of the functional synchrony between brain regions independent of a specific task, is being increasingly used to examine functional circuits in ADHD.[38,39] Findings of increased orbitofrontal connectivity with striatum and anterior cingulate cortex (ACC) in ADHD relative to comparisons are particularly relevant to emotion regulation.[40] However, iFC linked specifically to emotion regulation deficits or to amygdala-based circuitry in ADHD has not been previously examined.

The present study examines how amygdala iFC relates to emotional lability (EL) in children with combined-type ADHD (ADHD-CT). Here, we define EL as the tendency to display rapidly changing emotions. We test the hypothesis that high parent ratings of EL in a large sample of children with ADHD are dimensionally associated with altered iFC between the amygdala and PFC, even after controlling for levels of behavioral dyscontrol, as assessed by ratings of hyperactive-impulsive symptoms. We control for hyperactivity given the high correlation with emotional impulsivity ($r = 0.62$) in youth with ADHD.[6] Furthermore, unlike inattention, hyper-activity, and emotion dysregulation have been found to decline in parallel from preschool to early school age,[41] suggesting a shared developmental trajectory. As a secondary means to disentangle the relationship between amygdala iFC and EL, we then establish subgroups of ADHD-CT youth selected for high versus low EL, and compare each to a group of typically developing comparisons (TDC) who have low EL, by definition. We predict that TDCs will differ from the high-EL ADHD subgroup, but not the low-EL ADHD subgroup. We also predict that differences in amygdala iFC will be larger between groups that differ in EL (high-EL ADHD versus TDC) compared to those that differ only on ADHD status (low-EL ADHD versus TDC), further supporting the specific link between amygdala iFC and EL. We note the theoretical advantage of obtaining a high-EL comparison group without ADHD for analyzing the interaction between diagnosis and EL severity. However, we were unable to recruit such children, as ADHD comorbidity is common in children with high EL, and we could not detect high EL in children without psychiatric comorbidities.

METHOD

Participants

We included 63 children with a diagnosis of ADHD-CT (aged 9.2 ± 2.0 years, 50 male and 13 female) who successfully completed both the behavioral and MRI protocols of a larger ongoing study of ADHD (Table 1). In all, 85 participants completed scans and 17 were excluded, before group assignment, from further analyses based on maximum head

displacement (>3 mm). An additional 5 were excluded because of excessive mean framewise displacement (>0.25 mm), resulting in the final sample. Participants were recruited on the basis of ADHD symptoms, unrelated to emotional disturbances: thus, the sample had widely distributed EL scores. Children were recruited from those seeking or receiving clinical services at the NYU Child Study Center and through Web and community postings to the general public. All children were right-handed and free of MRI contraindications. Children meeting diagnostic criteria for current major depression, or pervasive developmental disorders, psychosis, substance use disorders, bipolar disorder, or Full Scale IQ <80 were excluded. Current comorbid *DSM-IV-TR* diagnoses were identified in 17 individuals: oppositional defiant disorder (ODD) (n = 14), anxiety disorder NOS (n = 2), generalized anxiety disorder (n = 1), obsessive compulsive disorder (n = 1), dysthymic disorder (n = 1), enuresis (n = 3), encopresis (n = 2), and tic disorders (n = 1).

Forty-four children (69%) with ADHD-CT were naive to psychotropic medications. Sixteen children (25%) were taking psychotropic medications during the study period; 14 were taking stimulants, which were suspended for at least 24 hours before the scan, and 1 was taking a nonstimulant plus an antidepressant and another took only a non-stimulant treatment for ADHD. Two participants taking stimulants were also taking combinations of nonstimulant ADHD treatments (n = 1) or antidepressants (n = 1), at the time of the scan. All parents or guardians provided written informed consent as approved by the New York University (NYU) School of Medicine Institutional Review Board. Children provided written assent. Families received financial compensation for participation.

To further assess the specificity of amygdala iFC deficits to EL, in a secondary analysis, functional magnetic resonance imaging (fMRI) data were obtained from 26 TDC children with no *DSM-IV-TR* Axis I diagnosis. Seven of these children were excluded because of excessive movement (mean framewise displacement >0.25), resulting in a final sample of 19 children. Study exclusions were the same as for the children with ADHD, and the groups were matched for sex and age.

Assessments

For all participants, the presence or absence of ADHD and comorbid diagnoses was determined by licensed psychologists/psychiatrists or by supervised postdoctoral fellows based on the results of diagnostic evaluations conducted with the Kiddie SADS–Present and Lifetime Version[42] semistructured interview of parents and children. Cases were regularly presented at weekly case conferences at which diagnostic consensus was achieved. Diagnostic procedures integrated K-SADS parent and child reports, school reports, prior mental health records, as well as teacher feedback on the Conners' Teacher Rating Scale–Revised, Long Version (CTRS-R:L[43]), which was available for 89% of the sample. Estimates of intelligence were obtained using an abbreviated IQ screener.[44] A parent also completed the Conners' Parent Rating Scale–Revised, Long Version (CPRS-R:L[43]). Age- and sex-adjusted t scores were calculated for each subscale (possible scores = 38–90; mean = 50).

For the purposes of this study, we indexed EL using the Emotional Lability (J Scale) of the CPRS-R-L Global Index. This scale comprises the items: "Temper outbursts," "Cries often and easily," and "Mood changes quickly and drastically." This scale has been normed in nearly 2,000 male and female individuals aged 6 to 17 years, with high internal consistency coefficients (0.7) and 6- to 8-week test–retest reliability (0.7).[43] High discriminant validity was established between youth with ADHD, those with clinically derived "emotional problems" and a nonclinical sample.[43] The scale has been used extensively in recent research as a measure of emotional problems.[15, 45–47] The CPRS-R-L Hyper-activity subscale (C Scale) was used as a covariate to control for symptoms of behavioral

dysregulation. Although EL is typically less highly correlated with inattention, supplementary findings used both inattention and hyperactivity as covariates, as indexed by the CPRS-R-L DSM Scale (N Scale).

MRI Data Acquisition

Imaging data were collected on a 3.0 Tesla Siemens Allegra at the NYU Center for Brain Imaging. Each participant completed at least one 6.5-minute resting-state fMRI scan within a 45-minute session to collect iFC data. These functional scans were collected using a customized multi-echo echo planar imaging (EPI) sequence (repetition time [TR] = 2,000 ms; effective echo time [TE] = 33 ms; flip angle = 90°, 33 slices, matrix = 64 × 64; field of view [FOV] = 240 × 192 mm; acquisition voxel size = 3 × 3 × 4 mm; number of volumes = 197). For spatial normalization and localization, high-resolution T1-weighted anatomical scans were acquired using a magnetization prepared gradient-echo sequence (TR = 2,530 ms, TE = 4.35 ms, inversion time = 1100 ms, flip angle = 7°, 128 slices, field of view = 256 mm, voxel size = 1.3 × 1.3 × 1 mm). Because of the ongoing study design, 2 sets of instructions were used: some participants were asked to keep their eyes open during the scans (viewing a black screen with a centered fixation cross), whereas others were asked to keep their eyes closed (Table 1). Given its potential impact on iFC indices, eye status was included as a covariate in all group-level analyses.

Image Preprocessing

For participants with more than 1 iFC scan within a session, the scan with the smallest amount of maximum calculated motion was selected for analysis. For the majority of subjects (96%), the first scan was used. Only scans with less than 3 mm of maximum head displacement in any axis were analyzed. As micromovements have been shown to potentially introduce artifactual correlations, mean framewise displacement (FD) was also computed, per recently described methods.[48] Subjects with mean FD >0.25 mm were excluded from further analyses and each subject mean FD was included as a covariate in group-level analyses. Groups did not differ on mean FD (Table 1), and mean FD was not correlated with EL scores for ADHD or typically developing comparisons.

Preprocessing techniques were completed using AFNI (http://afni.nimh.nih.gov) and FSL software (www.fmrib.ox.ac.uk). Preprocessing consisted of the following; slice time correction for interleaved acquisitions using Fourier interpolation; 3-dimensional motion correction using least-squares alignment of each volume to the mean image using Fourier interpolation; despiking of extreme time series outliers using a continuous transformation function; temporal band-pass filtering between 0.009 and 0.1 Hz using Fourier transformation; spatial smoothing (Gaussian kernel full width at half maximum = 6 mm); mean-based intensity normalization of all volumes by the same factor; and linear and quadratic detrending. Nuisance signals from 6 motion parameters, white matter, and cerebrospinal fluid (derived from appropriate masks), and the global signal (mean across all voxels in the brain) were removed to control for movement and physiological processes (e.g., fluctuations related to cardiac and respiratory cycles and large-scale neural signals). Linear registration of the high-resolution structural images to the MNI152 template was carried out using the FSL tool *FLIRT* with 12 degrees of freedom (df) and refined using *FNIRT* nonlinear registration. Linear registration of each participant's functional time series to the high-resolution structural image was performed using FSL's *FLIRT* (6 df). Functional-to-anatomical co-registration was improved by intermediate registration to a low-resolution image and b0 unwarping. These preprocessing steps resulted in a 4-dimensional (4D) residual functional volume in native functional space, for each participant. For group comparisons, each participant's 4D residual volume was spatially normalized by applying the calculated transformation to MNI152 standard space (2 × 2 × 2-mm resolution).

Region-of-Interest Selection

We defined regions-of-interest (ROIs) representing the whole amygdala bilaterally based on the Juelich histological atlas implemented in FSL. Similar to prior work,[49] we used masks that included all voxels with a minimum 50% likelihood of being correctly located in the amygdala. We considered analyzing individual subdivisions of the amygdala, as we have done previously in adults and adolescents.[49, 50] However, given the young age of our sample and the lack of research on the iFC of amygdala subdivisions in typical children or those with ADHD, we chose a whole-amygdala approach.

Participant Level Analyses

Left and right amygdala time series were extracted from the 4D preprocessed resting state scan in MNI152 standard space by separately averaging across all voxels in each ROI. Next, we calculated the correlation between these time series and those of each voxel in the preprocessed resting state scan in native space. This analysis was implemented using 3dfim+ (AFNI). Individual participant-level correlation maps were converted to Z-value maps using Fisher's r-to-z transformation and then transformed into MNI152 2mm standard space. This analysis produced subject-level maps of voxelwise correlations with the time-series of the left and right amygdala ROIs.

Group-Level Analyses

First, group-level mixed-effects analyses were carried out using FSL FEAT for the right and left amygdala ROI for all ADHD participants. Our main analysis included demeaned CPRS-R:L EL T-scores as the primary variable of interest, and sex, age, mean FD, and eye-status (open/closed) as nuisance covariates. Because the aim of the study was to examine EL iFC independent of symptoms of behavioral dysregulation, demeaned scores on the CPRS-R:L Hyperactivity scale were also included in the model. In supplementary analyses, overall DSM ADHD symptoms (inattention + hyperactivity) were used as a covariate instead of hyperactivity, to confirm the specificity of the findings to EL and not to other symptoms of ADHD. Corrections for multiple comparisons were carried out at the cluster level using Gaussian random field theory (voxel-wise: minimum Z score >2.3; cluster significance: $p < 0.05$, corrected). This group-level analysis produced thresholded Z-score maps indicating clusters where iFC with each ROI was significantly related to EL scores.

To further confirm the specificity of our findings, iFC in clusters showing a significant relationship between EL and amygdala iFC was then compared to that of TDCs (n = 19). To this end, we extracted 2 subgroups from the ADHD group (n = 63) used in the primary analysis: participants with EL T scores in the clinically significant range (>65) comprised the high-EL group (n = 18); and a demographically matched group (n = 20) with nonclinical EL T scores (<55) comprised the low-EL group. Because there were more participants with scores in the low than in the high-EL range, 26 were pseudorandomly excluded, blinded to EL score, to allow for age and gender matching and similarly sized groups. EL T scores were significantly different ($p < .0001$) between the 2 ADHD groups.

We extracted the average Fisher's Z correlation co-efficients for significant EL-iFC clusters from the initial ADHD-only EL analyses from each participant's preprocessed resting state scan in MNI152 standard space. These correlation coefficients were averaged across clusters such that 3 values (left amygdala positive contrasts and right and left amygdala negative contrasts) were used for group comparisons. Because the iFC measures were derived based on the EL scores in the ADHD group, univariate analyses of variance including all 3 groups (high-EL ADHD, low-EL ADHD, and low-EL TDCs) would have necessarily been significant. Thus, we conducted independent-sample t tests (SPSS 19.0; IBM, Chicago, IL) between TDCs and each of the 2 ADHD groups. Comparisons between the low- and high-

EL groups were not examined for the same reason that an analysis of variance was not used. To account for the 3 between-group comparisons, a Bonferroni-corrected statistical threshold was applied ($p < .017$). Measures of effect size were obtained from independent samples t tests comparing the TDC group to the low- and high-EL ADHD groups on the three measures of amygdala iFC (SPSS 19.0; IBM, Chicago, IL). Using previously published methods,[51,52] we compared the effect sizes of these group comparisons using a z test to test the hypothesis that group differences in amygdala iFC would be less for the groups that do not vary on EL (low-EL ADHD-TDC comparison) than those that do (high-EL ADHD-TDC comparison).

Finally, to address the possibility that ODD co-morbidity was driving our EL findings, mean amygdala iFC from clusters found to be significantly associated with EL was compared between the ADHD participants with (n = 14) and without (n = 49) ODD, using an independent-samples t test.

RESULTS

Characteristics for the full ADHD group, the 2 ADHD subgroups and the TDC group included in the secondary analyses are presented in Table 1. As designed, EL scores differed between ADHD groups and between the high-EL ADHD and the TDC group. TDCs also showed significantly lower hyperactivity scores than either ADHD subgroup, although the high- and low-EL ADHD subgroups did not differ on hyperactivity scores. The 3 groups did not differ in regard to age ($F_{2,54}$ =1.5, $p = .24$), sex ($F_{2,54} = 0.99$, $p = .038$), IQ (F[2,53] = 3.18, $p = .05$), or movement parameters (maximum head displacement: $F_{2,54} = 1.0$, $p = .37$; framewise displacement: $F_{2,54} = 1.4$, $p = .25$) and the 2 ADHD groups did not differ in diagnostic comorbidity (15% versus 22%; $p = .62$)

Amygdala IFC and Emotional Lability in ADHD

While controlling for hyperactivity, EL scores were positively associated with iFC between left amygdala and medial PFC regions including rostral anterior cingulate cortex (rACC) and frontal pole (Table 2 and Figure 1) in children with ADHD. EL scores were also negatively associated with left amygdala–bilateral insula/superior temporal gyrus (STG) iFC as well as right amygdala–bilateral posterior insula iFC (Table 2 and Figure 1). In this case, high EL was associated with decreased positive iFC between both amygdala seeds and the bilateral insula/STG clusters (Figure 1). When hyperactivity and inattention were both used as covariates, findings were nearly identical to those found when hyperactivity was the only covariate (Figure S1). When divided into groups based on the presence or absence of comorbid ODD, iFC did not differ between the groups for any of the clusters (all $p > .05$).

Group Amygdala iFC Comparisons

To further test the specificity of altered amygdala iFC to EL, we conducted t tests to examine differences between low-EL ADHD and TDC and between high-EL ADHD and TDC and compared their effect sizes. Amygdala iFC did not differ between the low-EL and TDC groups for any of the clusters assessed (Figure 2). We found a trend toward significantly greater positive left amygdala–ACC iFC for the high-EL group compared to the TDCs ($t_{35} = -2.30$, $p = .027$; Figure 2). The high-EL group also exhibited a trend toward decreased iFC relative to the TDC group between the left amygdala and insula/STG (t[35] = 2.30, $p = .028$) and between the right amygdala and the insula/STG clusters (t[35] = 2.02, $p = .051$; Figure 2). Effect sizes for the low-EL versus TDC were significantly smaller than those for the high-EL versus TDC for each of the 3 clusters (left amygdala–ACC: z = 4.12, $p < .001$; left amygdala–insula/STG: z = 4.72, $p < .0001$; right amygdala–insula/STG: z = 2.63, $p < .0001$).

DISCUSSION

In a large sample of 6- to 13-year-old children with ADHD, iFC of a corticoamygdalar network was related to parent ratings of emotional lability. Controlling for hyperactivity, high levels of EL were specifically associated with increased positive iFC between bilateral amygdala and medial prefrontal regions and less positive iFC between amygdala and bilateral insula/STG, suggesting a disruption in emotional control networks in a subset of children with ADHD. Accounting for inattention as well as hyperactivity yielded very similar results to hyperactivity alone, further highlighting the specificity of these results EL and not to other symptoms of ADHD. The relationship between amygdala iFC and EL was further supported by a subgroup analysis that showed that amygdala iFC in the low-EL group did not differ from that of the comparison group, as would be expected, as the groups did not differ on EL. Thus, the group differences on hyperactivity scores appeared to have no effect on amygdala iFC. Larger effects were observed when comparing the high-EL and TDC groups, which would be predicted because of group differences in EL. These large effect sizes observed between high-EL and TDC iFC comparisons (range = 0.66–0.76), suggest that these subgroup analyses did not meet statistical significance because they were underpowered to detect group differences. Because ODD diagnoses were equivalent between the high- and low-EL groups, and because our results did not differ between groups with and without ODD, this co-morbidity is unlikely to have driven our findings. Subthreshold mood and anxiety symptoms recorded as “NOS” cases were rare and therefore also unlikely to account for these findings.

Study hypotheses regarding altered iFC between the amygdala and cortical regions were supported. Our results suggest that elevated positive amygdala-PFC iFC is associated with difficulty in regulating the expression of negative emotions. These findings are consistent with theories of emotional perception where amygdala and rostral ACC are involved in the identification of emotional significance and generation of affective responses.[53] More recent task-based studies in adults suggest that the interactions between medial PFC/rostral ACC and amygdala specifically play a role in affect regulation, particularly in relation to negative emotions.[54]

In addition, regions in bilateral posterior insula extending into temporal cortex emerged as having significantly decreased positive iFC with the amygdala in ADHD youth with higher EL. Although we did not specifically predict findings in the insula, this region is structurally connected with the amygdala and with other limbic and cortical association areas. Intrinsic functional connectivity and activation of the posterior insula have been associated with emotion, interoception, and perception,[55,56] particularly perception of one’s own emotions. Strokes localized to the posterior insula have also been reported to result in impaired processing of valence and intensity of negative facial expressions and words.[57] The emerging evidence of the posterior insula’s involvement in emotional processing raises the possibility that a failure in emotional perception and related action may partly underlie observed emotion dysregulation in ADHD.

Our findings should be interpreted in light of several limitations. First, we were unable to recruit and to study typically developing children with high EL. Despite the theoretical interest, recruiting such children is not practical. ADHD comorbidity is overwhelmingly present in children with high EL,[17] and we could not detect high EL in children lacking other psychiatric disorders. Accordingly, we were unable to stratify controls according to high- and low-EL status, because of the lack of variability in their EL scores. Second, we were not able to test whether EL-related alterations in amygdala circuits are unique to children with ADHD or are also observed in other disorders characterized by high EL such as ODD or depression. Future studies comparing EL and amygdala iFC between diagnoses

are needed. Third, to confirm this circuit's involvement in emotion regulation in childhood, additional work involving self-report and active experimental manipulation of emotion regulation will be required. Finally, although most children were drug treatment naive, and nearly all of those currently treated were off medications when scanned, we cannot completely exclude the possibility that prior pharmacotherapy may have affected iFC findings.

In summary, children with ADHD who are impaired by high EL exhibited aberrant iFC in regions associated with emotion regulation when examined dimensionally. These findings are unlikely to be ascribable to hyperactivity as evidenced by greater differences between groups differing on EL and hyperactivity (high-EL versus TDC) than between groups differing only on hyperactivity, and not EL (low-EL versus TDC). This suggests that a subset of youth with ADHD have specific disruptions in amygdala networks that underlie emotion regulation impairments. Furthermore, resting-state functional connectivity appears to be suitable for detecting emotion-relevant differences in iFC in youth with ADHD. Our findings validate the need for further research focused on emotion regulation difficulties in a subgroup of children with ADHD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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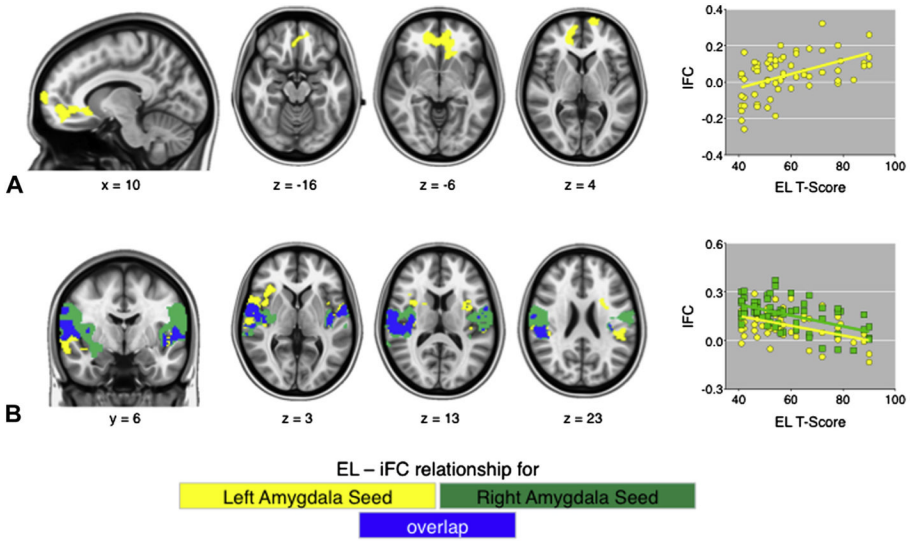

FIGURE 1.

Direction of the relationship between dimensional parent emotional lability (EL) ratings, co-varying for hyperactivity, and extracted time-series values for the significant clusters are shown in the scatter plots. Note: Images in row A demonstrate that increased EL is associated with increased amygdala connectivity (“iFC”) with the highlighted prefrontal regions, whereas row B shows that increased EL (“EL T-score”) is associated with decreased amygdala–insula/STG connectivity (“iFC”). Scatter plots address EL T-scores (x-axis) versus amygdala correlations (y-axis).

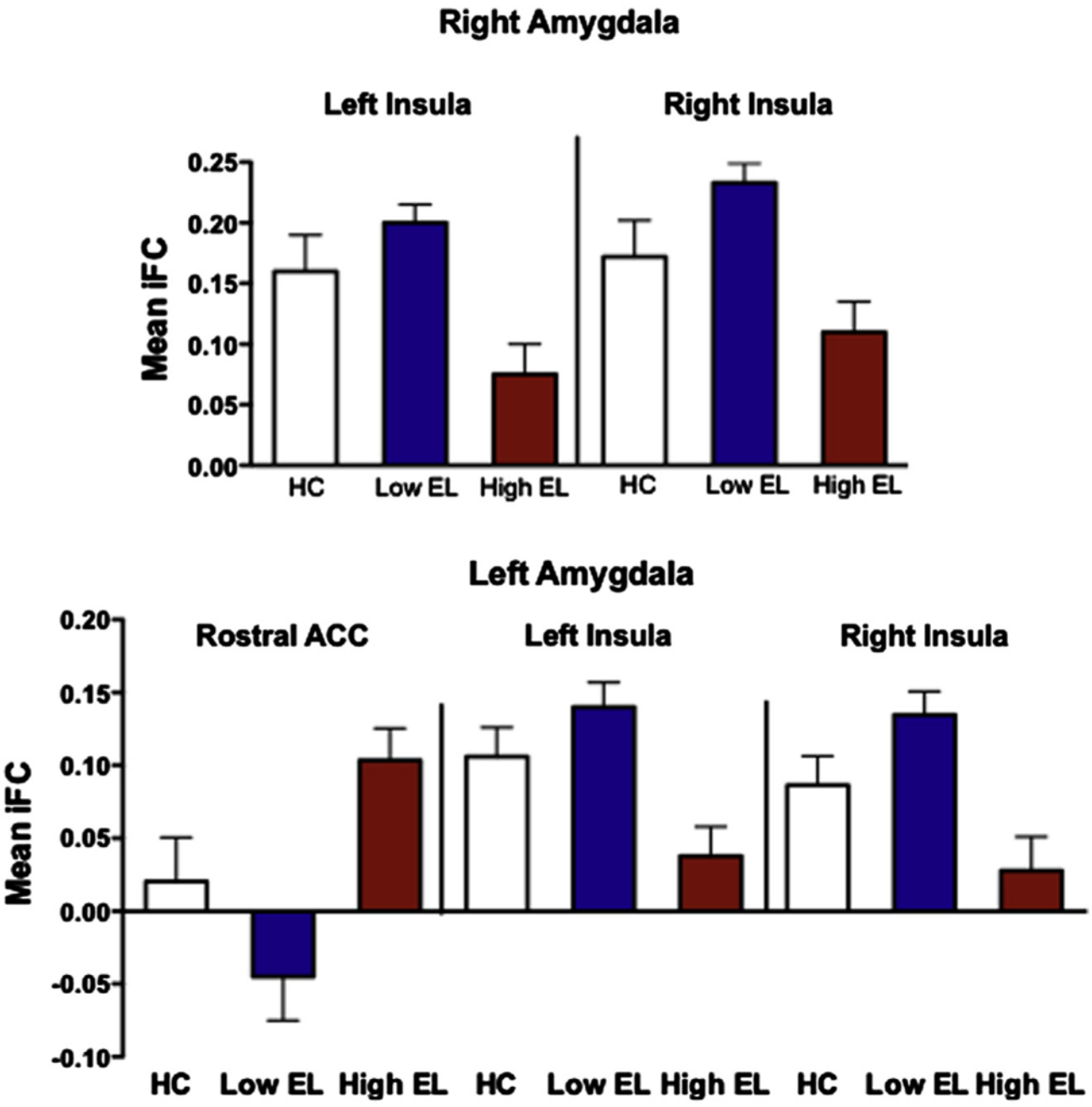

FIGURE 2.

Mean correlation coefficients between each of the amygdala seeds and the significant cortical regions (derived from the initial attention-deficit/hyperactivity disorder [ADHD]–only analyses) displayed for each of the groups. Note: Error bars indicate SD. IFC = intrinsic functional connectivity; rACC = rostral anterior cingulate cortex; SFG = superior frontal gyrus; STG = superior temporal gyrus.

TABLE 1

Clinical and Demographic Characteristics of the Attention-Deficit/Hyperactivity Disorder (ADHD) Group Used for the Dimensional and Subgroup Analysis

	ADHD-CT (n = 63)	High EL (n = 18)	Low EL (n = 20)	TDC (n = 19)
Male, n (%)	50 (79)	16 (89)	14 (70)	15 (79)
Age, y	9.4 (2.0)	9.9 (1.6)	9.5 (1.9)	10.5 (1.9)
Eyes, n open (%)	28 (44)	8 (44)	13 (65)	11 (58)
Race, n (%)				
White	29 (46)	7 (39)	8 (40)	12 (63)
African American	10 (16)	5 (28)	5 (25)	4 (21)
Asian Pacific Islander	4 (6)	0 (0)	2 (10)	1 (5)
American Indian	0	0	0	0
Other	14 (22)	5 (27)	5 (25)	2 (11)
Mixed	6 (10)	1 (6)	0 (0)	0
Ethnicity, n (%)				
Hispanic	23 (37)	9 (50)	6 (30)	3 (16)
SES, n (%)				
1 (low)	4 (6)	1 (6)	1 (5)	2 (11)
2	7 (11)	4 (22)	2 (10)	0
3	7 (11)	3 (16)	3 (15)	3 (16)
4	21 (34)	5 (28)	5 (25)	6 (32)
5 (high)	24 (38)	5 (28)	9 (45)	8 (41)
Full Scale IQ	105.5 (14.6)	98.9 (16.8)	109.3 (13.5)	109.8 (13.7)
Maximum movement (mm)	1.33 (1.5)	1.15 (2.0)	1.88 (1.4)	1.88 (2.0)
Mean framewise displacement (mm)	0.13 (0.05)	0.13 (0.06)	0.14 (0.05)	0.17 (0.02)
CPRS-R: Emotional Lability Scale[a]	58 (14.6)	77.9 (8.5)	44.5 (4.2)	44.5 (4.3)
(range)	(41–90)	(65–90)	(41–54)	(41–55)
CPRS-R: Hyperactivity Scale[b]	72 (10.8)	76.5 (8.4)	71.8 (11.6)	45.9 (5.5)
(range)	(54–90)	(56–90)	(54–90)	(43–67)
Psychiatric comorbidity (%)	27	22	15	0

Note: Means and standard deviations (in parentheses) are presented for each group, unless noted otherwise. ADHD-CT = attention-deficit/hyperactivity disorder, combined type; CPRS-R = Connors Parent Rating Scale–Revised; EL = emotional lability; SES = socioeconomic status.

[a] CPRS-R Emotional Lability (EL) Scale parent ratings (t scores) differed between high-EL and low-EL groups ($t_{36} = 14.7$, $p < .0001$) and between typically developing comparisons (TDC) and the high-EL group ($t_{35} = -14.8$, $p < .0001$). Skewness = 0.82.

[b] Hyperactivity-impulsivity (t scores) ratings differed between each of the ADHD groups and the comparison group (High EL vs. comparisons: $t_{35} = -13.0$, $p < .0001$ and Low EL vs. comparisons: $t_{36} = -8.8$, $p < .0001$). No differences on hyperactivity scores were found between the high- and low-EL groups.

TABLE 2

Clusters With Significant Associations With Emotional Lability (EL) Scores

Right amygdala ROI	**Cluster Size**	**X**	**Y**	**Z**	**Max Z**	***p***
Negative relationship with EL						
Cluster 1: Posterior insula (L)	2,245	340	312	6	4.47	.0003
Parietal operculum		356	324	16	3.64	
Precentral gyrus		352	38	30	3.42	
		358	0	12	3.35	
Insula		334	322	24	3.06	
Cluster 2: Posterior insula (R)	4,400	62	38	32	4.91	.0001
		56	328	14	4.85	
		40	38	10	4.64	
		26	0	310	3.74	
Left amygdala ROI						
Positive relationship with EL						
Rostral ACC	1,329	18	48	2	4.00	.0043
		36	44	310	3.28	
Frontal Pole		314	72	10	3.60	
Negative relationship with EL						
Cluster 1: Superior temporal gyrus (L)	1,675	352	6	36	3.85	.0009
		324	6	28	3.74	
Insula		342	312	4	3.58	
		344	12	328	3.53	
		350	328	20	3.78	
Insula		338	8	10	3.02	
Cluster 2: Superior temporal gyrus (R)	3,238	66	320	8	4.64	.0001
Insula		38	318	10	4.11	
		42	32	310	3.88	
		34	8	14	3.52	
Post-central gyrus		66	38	34	3.34	
		60	4	4	3.34	

Right amygdala ROI	Cluster Size	X	Y	Z	Max Z	*p*
		36	26	6	3.23	

Note: Cluster size is represented by the number of voxels present in the cluster. X, Y, Z represent Montreal Neurological Institute (MNI) Coordinates for the cluster peak maximum Z values. ACC = anterior cingulate cortex; L = left; Max = maximum; R = right; ROI = region of interest.