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# Altered Lateral Prefrontal Cortex Functioning During Emotional Interference Resistance Is Associated With Affect Lability in Adults With Persisting Symptoms of Attention-Deficit/Hyperactivity Disorder From Childhood

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## ABSTRACT

**BACKGROUND:** Attention-deficit/hyperactivity disorder (ADHD) is a common neurodevelopmental disorder characterized by inattention and/or impulsivity/hyperactivity. ADHD, especially when persisting into adulthood, often includes emotional dysregulation, such as affect lability; however, the neural correlates of emotionality in adults with heterogeneous ADHD symptom persistence remain unclear.

**METHODS:** The present study sought to determine shared and distinct functional neuroanatomical profiles of neural circuitry during emotional interference resistance using the emotional face n-back task in adult participants with persisting ($n$ = 47), desisting ($n$ = 93), or no ($n$ = 42) childhood ADHD symptoms while undergoing functional magnetic resonance imaging.

**RESULTS:** Participants without any lifetime ADHD diagnosis performed significantly better (faster and more accurately) than participants with ADHD diagnoses on trials with high cognitive loads (2-back) that included task-irrelevant emotional distractors, tapping into executive functioning and emotion regulatory processes. In participants with persisting ADHD symptoms, more severe emotional symptoms were related to worse task performance. Heightened dorsolateral and ventrolateral prefrontal cortex activation was associated with more accurate and faster performance on 2-back emotional faces trials, respectively. Reduced activation was associated with greater affect lability in adults with persisting ADHD, and dorsolateral prefrontal cortex activation mediated the relationship between affect lability and task accuracy.

**CONCLUSIONS:** These findings suggest that alterations in dorsolateral prefrontal cortex function associated with greater interference in cognitive processes from emotion could represent a marker of risk for problems with emotional dysregulation in individuals with persisting ADHD and thus represent a potential therapeutic target for those with greater emotional symptoms of ADHD.

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Attention-deficit/hyperactivity disorder (ADHD) is a prevalent, heterogeneous neurodevelopmental disorder characterized by inattention and/or impulsivity/hyperactivity (1). Current diagnostic criteria emphasize cognitive symptoms of the disorder; however, emotional symptoms (e.g., affect lability, anger/irritability) are highly prevalent in both children (25%–45%) and adults (30%–70%) with ADHD (2). Notably, emotional symptoms in ADHD confer an additional risk for comorbid psychiatric disorders (e.g., depression), further impair functionality, and are associated with worse clinical outcomes than in cases without such symptoms (3–5). Emotional symptoms can be used to predict patient outcomes over and above classic symptoms of inattention and impulsivity/hyperactivity, but the confluence of various cognitive and affective dimensions also contributes to the complex clinical heterogeneity of ADHD (6–8). Despite burgeoning evidence centering on emotional symptoms as common features of ADHD etiology (6,9), understanding of the neurobiological mechanisms and processes underpinning the affective dimensions of ADHD is sparse, particularly in adult populations. This study aimed to address this gap by elucidating patterns of neural functioning in emotion regulation circuitry across individuals with varying levels of symptom persistence into adulthood to deepen understanding of the neural pathoetiology of ADHD.

One primary cognitive process of voluntary emotion regulation involves the ability to modulate attention toward or away from emotional information (10,11). ADHD is characterized by difficulty with modulating attention in the context of goal-

 

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directed behavior. Evidence suggests that individuals with ADHD, relative to those without, perform significantly worse on cognitive (e.g., working memory) tasks when instructed to ignore emotional distractors (i.e., task-irrelevant, affectively charged interference) (12,13). For instance, Marx *et al.* (12) showed that participants with ADHD exhibit emotional interference control deficits even for low salience (less charged) emotional distractors, whereas participants without ADHD exhibit performance deficits only for highly charged emotional stimuli, suggesting a lower threshold for affective distractibility in ADHD. One such cognitively demanding task with emotional distractors is the emotional face n-back (EFNBACK) task, which has been used to test cognitive-affective symptoms across psychiatric disorders (e.g., depression, bipolar disorder, and pediatric ADHD), while participants undergo functional magnetic resonance imaging (fMRI) scanning (14–16). Briefly, the task features low and high cognitive load (0-back and 2-back conditions, respectively) and 4 types of distractors in the form of emotional faces (details in Methods and Materials). The EFNBACK task is thus well suited to examine the functioning of neural circuitry implicated in voluntary emotion regulation as it relates to emotional symptoms of ADHD.

Brain structures involved in the detection of emotional information, henceforth the affective salience network, include the amygdala—a complex of distinct yet interconnected nuclei involved in salience detection and valence encoding (17,18)—as well as cortical structures, such as the rostral anterior cingulate cortex (rACC) and the ventromedial prefrontal cortex (vmPFC), which facilitate evaluation of emotional stimuli (11). Interactions between these medial frontal structures and the amygdala (sometimes referred to as mPFC-amygdala circuitry) are centrally implicated in emotion regulatory processes in humans and animal models and are disrupted in affective psychopathological states characterized by internalizing symptoms (19–22). Whereas mPFC-amygdala circuitry is involved in aspects of emotion information detection, valence assignment, and rudimentary processing, additional cognitive control regions are thought to downregulate overexcited subcortical regions, dampening impulsivity (via striatal connections) (23,24) and affective reactivity (via amygdalar connections) (25,26). Specifically, lateral PFC regions, such as the dorsolateral PFC (dlPFC) and ventrolateral PFC (vlPFC), modulate reactive and/or habitual responses via effortful control by inhibiting prepotent responses and directing and sustaining attention on goal-relevant information (e.g., away from task-irrelevant distractors) (26–28).

Neuroimaging studies have found that directing attention away from negatively valenced emotional distractors (e.g., angry or sad faces) compared with neutral distractors (e.g., blank expression faces), for instance, is associated with heightened activation in the affective salience network and reduced activation in lateral PFC regions and weaker frontoamygdala functional connectivity (16,29). Researchers have interpreted these findings to indicate that attentional resources dedicated to performing the working memory task and supported by lateral PFC regions are momentarily commandeered by medial frontal and/or temporal structures responding to sensory information that draws attention toward the (often salient and biologically imperative) emotionally distracting stimuli (30). Consistent with this interpretation are findings showing that greater affective salience network activation and reduced lateral PFC (e.g., dlPFC) engagement is associated with worse cognitive performance (i.e., less accurate working memory) (30–35). In contrast, greater vlPFC recruitment has been linked to reduced subjective distractibility and emotionality felt toward negative affective stimuli (33) as well as better working memory performance in the presence of emotional interference (30,31,33,34). Critically, despite evidence that emotional symptoms of ADHD are linked with worse outcomes, few neuroimaging studies have examined the neural substrates of emotion regulation associated with emotional symptoms of ADHD in adults; this is likely due to the historical emphasis of studying ADHD as a developmental disorder.

The present study examined patterns of neural activation in adults with childhood ADHD diagnoses (and either persisting [ADHD-P] or desisting [ADHD-D] symptoms) and adults without any lifetime ADHD diagnosis (ADHD-NA) while undergoing fMRI scanning and performing the EFNBACK task. Our primary hypotheses focused on 2-back emotional faces (EF+/ER+) trials to examine effortful cognitive control during emotional interference, which recruits executive functioning and emotional regulatory processes. First, we hypothesized that more severe ADHD symptoms (ADHD-P > ADHD-D/ADHD-NA) would be associated with worse overall performance in terms of task accuracy. Second, we hypothesized that heightened activation in affective salience regions (i.e., amygdala, rACC, vmPFC) and reduced cognitive control regional activation (i.e., dlPFC, vlPFC) would be associated with reduced EFNBACK accuracy. Third, we hypothesized significantly greater recruitment of affective salience regions and significantly less engagement of cognitive control regions in the ADHD-P group compared with the ADHD-D and ADHD-NA groups during EF+/ER+ trials. Finally, in the ADHD-P group, in whom we expected higher emotional symptoms to be exhibited, we hypothesized that heightened activation in affective salience regions and/or reduced cognitive control regional activation during 2-back condition with emotionally salient distractors (EF+/ER+) would be associated with more affect lability. To additionally test the extent to which functional activation of the relevant neural region explained the association between emotional symptoms and task performance, we conducted an exploratory statistical mediation analysis. That is, although previous work has linked emotional symptoms and cognitive performance in ADHD, we wanted to examine the extent to which activation in implicated neural regions explained the relationship between emotional symptoms and EFNBACK task performance in adults with persisting ADHD symptoms.

## METHODS AND MATERIALS

### Participants

The initial sample in the present study consisted of 256 participants who were recruited into the study from the Pittsburgh ADHD Longitudinal Study (PALS), a sample of individuals diagnosed with ADHD (per DSM-III-R or DSM-IV criteria) as children between 1987 and 1996 using comprehensive, standardized, multi-informant diagnostic methods including clinician consensus (36,37). Of the 256 participants, 182 provided usable fMRI data (criteria described in Neuroimaging Data and

in the Supplement), which included participants with persisting ADHD symptoms (ADHD-P, *n* = 47; mean [SD] age = 34.74 [3.87] years; 85.1% male), participants with desisting ADHD symptoms (ADHD-D, *n* = 93; mean age = 34.81 [3.26] years; 93.5% male), and participants without a childhood ADHD diagnosis (ADHD-NA, *n* = 42; mean age = 35.57 [3.75] years; 85.7% male). Table 1 lists characteristics of participants.

Exclusion criteria for the present study included MRI scanning contraindications (e.g., nonremovable metal, claustrophobia), diagnoses of neurological disorders (e.g., seizures, meningitis, or encephalitis) or conditions (e.g., concussion with loss of consciousness >5 minutes), certain psychiatric disorders (e.g., schizophrenia, psychosis, severe substance use disorder per DSM-5 excluding tobacco), certain medications (e.g., blood pressure medications), and weight >300 lb.

**Table 1. Demographic Characteristics of Participants**

| Clinical Measure | *n* (%) |
|---|---|
| Sex, Male | 163 (89.6%) |
| Race | |
| American Indian or Alaskan Native | 2 (1.1%) |
| Asian | 1 (0.6%) |
| Black or African American | 24 (13.2%) |
| More than one race | 11 (6.0%) |
| Native Hawaiian or other Pacific Islander | 0 (0%) |
| White | 141 (77.5%) |
| Unknown or not reported | 3 (1.7%) |
| Ethnicity | |
| Hispanic or Latino | 2 (1.1%) |
| Not Hispanic or Latino | 166 (91.2%) |
| Unknown or not reported | 14 (7.7%) |
| Education | |
| Less than high school | 1 (0.6%) |
| Attended high school but did not graduate | 3 (1.7%) |
| High school graduate or GED equivalent | 29 (15.9%) |
| Completed technical/secretarial or other specialized training | 13 (7.1%) |
| Partial college (at least 1 year) | 29 (16.0%) |
| Associate or 2-year degree | 31 (17.0%) |
| College or university graduate | 49 (26.9%) |
| Graduate or professional training (graduate degree) | 27 (14.8%) |
| Monthly Income | |
| $0 | 9 (4.9%) |
| Less than $200 | 4 (2.2%) |
| $200–$499 | 5 (2.7%) |
| $500–$999 | 20 (11.0%) |
| $1000–$1999 | 30 (16.5%) |
| $2000–$2999 | 37 (20.3%) |
| $3000–$4999 | 34 (18.7%) |
| $5000–$6999 | 22 (12.1%) |
| $7000 or more | 21 (11.5%) |
| ADHD Symptom Persistence | |
| Persisting | 47 (25.8%) |
| Desisting | 93 (51.1%) |
| No ADHD history | 42 (23.1%) |

ADHD, attention-deficit/hyperactivity disorder; GED, General Educational Development (test).

Participants prescribed stimulant medications (*n* = 11) were required to refrain from taking medication for 24 hours before the MRI scan session, and participants who smoked were asked to abstain from smoking for 2 hours before the scan (see the Supplement for tobacco use breakdown). Additional details on the PALS neuroimaging sample can be found in previous publications (38,39).

## Procedure

After obtaining informed consent and screening for drugs/alcohol using saliva-based testing, participants practiced scanner tasks in an MRI simulator to familiarize themselves with the neuroimaging protocol (see the Supplement for substance use breakdown). Following an out-of-scanner practice session, participants completed the neuroimaging protocol, cognitive tasks, and questionnaires (details in Neuroimaging Data, EFNBACK Task, and Cognitive and Emotional ADHD Symptoms). This research was approved by the University of Pittsburgh Human Research Protections Office.

## Neuroimaging Data

**Acquisition.** Neuroimaging data were acquired on a 3T MRI scanner that was upgraded from a Siemens MAGNETOM Trio to a Siemens MAGNETOM Prisma (Siemens Healthineers) (3T Trio, *n* = 116; 3T Prisma, *n* = 66). We harmonized the datasets using neuroCombat (https://github.com/Jfortin1/neuroCombat) to account for collecting neuroimaging data on an MRI scanner before and after the upgrade and included ADHD group membership (i.e., ADHD-P, ADHD-D, ADHD-NA) as a covariate to pool data while preserving relevant biological variability of interest (40). See the Supplement for MRI scan acquisition details and preprocessing procedures.

**Region-of-Interest Definitions.** Regions of interest (ROIs) in cortico-amygdala regions were chosen to represent 2 aspects of emotional regulatory processes involved in resisting valenced distractors; these included top-down control regions in the lateral PFC (specifically, dlPFC and vlPFC) and structures constituting an affective salience network, which included the vmPFC, rACC, and centromedial and basolateral amygdala. All 6 ROIs were defined using the Brainnetome atlas and included both left and right hemispheres (41). See the Supplement for specific ROI definitions and Figure 1 for an illustration of the ROIs on a standard brain template.

## EFNBACK Task

The EFNBACK task is a modified visual sequential letter working-memory n-back task with emotional faces presented as distractors (42). As a neuroimaging task, the EFNBACK has elicited neural activation in regions associated with emotion regulation in several neuropsychiatric disorders (14,42,43), underscoring its ability to discriminate functional differences across psychopathologies. See the Supplement for task details. Given our interest in neural systems of regulation in the context of emotional interference resistance in adult ADHD groups, we focused our analyses on the conditions that included (neutral, negative, or positive) faces. We refer to this combination of trials, which include high cognitive and affective loads, as EF+/ER+ to identify these trials as aimed at

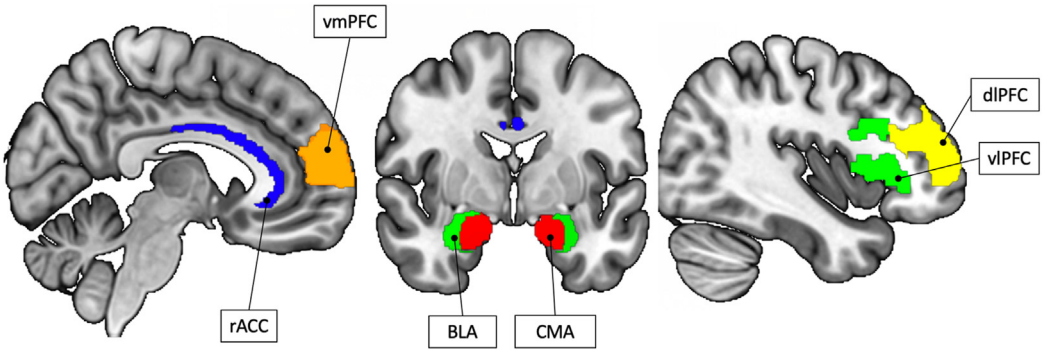


**Figure 1.** Regions of interest defined using the Brainnetome atlas. BLA, basolateral amygdala; CMA, centromedial amygdala; dlPFC, dorsolateral prefrontal cortex; rACC, rostral anterior cingulate cortex; vlPFC, ventrolateral PFC; vmPFC, ventromedial PFC.

engaging processes related to executive functioning and emotion regulation, respectively. The EFNBACK behavioral measures of interest were accuracy, defined as the percent of total correct trials, and response times, defined as the length of time (in milliseconds) participants took to respond on correct trials. See Figure 2A, B for distributions of EFNBACK accuracy and response times, respectively.

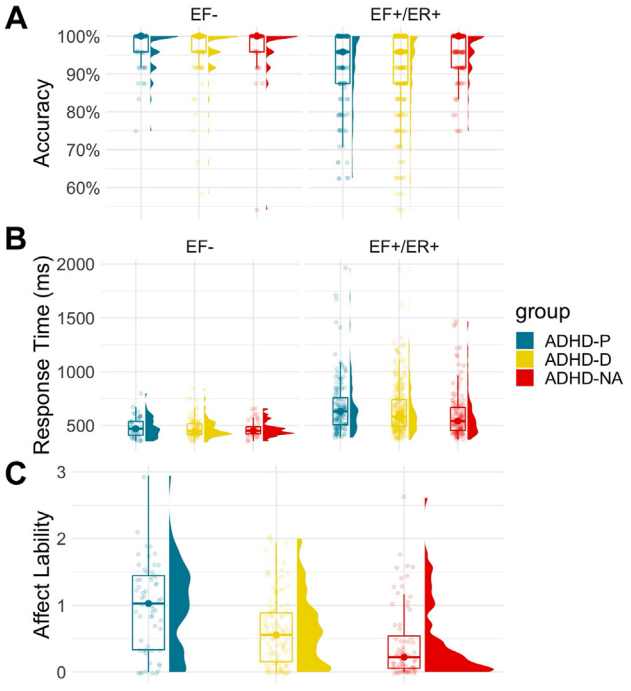


**Figure 2.** Distribution of Emotional Face n-back task trial **(A)** mean accuracy and **(B)** response times on correct trials. **(C)** Distribution of 18-item Affect Lability Scales score for each group. ADHD, attention-deficit/hyperactivty disorder; ADHD-D, adults with desisting ADHD symptoms; ADHD-NA, adults with no history of ADHD symptoms; ADHD-P, adults with persisting ADHD symptoms; EF−, 0-back no emotional faces trials; EF+/ER+, 2-back emotional faces trials.

### Cognitive and Emotional ADHD Symptoms

ADHD (cognitive) symptoms during adulthood were assessed using mean scores from the Barkley Adult ADHD Rating Scale–IV (44). As described in previous publications using this sample (38,39), the Barkley Adult ADHD Rating Scale–IV is an 18-item questionnaire with responses ranging from 0 to 3. ADHD symptoms were persistent if 5 or more symptoms of inattention or impulsivity/hyperactivity were present, consistent with DSM-5 criteria. Symptoms were considered present by taking the higher response from either self-report or collateral informant report to address potential underreporting. Barkley Adult ADHD Rating Scale–IV scores had excellent internal reliability (Cronbach's $\alpha = 0.95$). We used mean scores from the 18-item Affective Lability Scales (45) to assess shifts in mood on a 4-point Likert scale, ranging from "Very uncharacteristic of me" to "Very characteristic of me." Affective Lability Scales scores had excellent internal reliability across the entire sample (Cronbach's $\alpha = 0.93$). See Figure 2C for distributions of Affective Lability Scales scores by participant group.

## RESULTS

### Task Effects

**Behavioral.** There was no significant condition-by-group interaction effect on mean accuracy ($F_{2,627} = 2.226$, $p = .109$, $\eta^2 = 0.007$), but there were significant main effects of both group ($F_{2,627} = 8.469$, $p < .001$, $\eta^2 = 0.026$) and condition ($F_{1,627} = 30.465$, $p < .001$, $\eta^2 = 0.046$) on accuracy. Post hoc pairwise *t* tests revealed that participants in the ADHD groups were significantly less accurate than those in the ADHD-NA group (ADHD-P: Bonferroni $p < .001$; ADHD-D: Bonferroni $p = .017$) across conditions. There was no significant difference in trial accuracy across conditions between the ADHD-P and ADHD-D groups (Bonferroni $p = 1.0$). Post hoc tests also revealed that participants across groups were significantly more accurate on EF− than on EF+/ER+ trials ($p < .001$).

There was no significant condition-by-group interaction effect on response times for correct trials ($F_{2,627} = 0.697$, $p = .499$, $\eta^2 = 0.002$). There was also no significant main effect of group on correct trial response times ($F_{2,627} = 2.976$, $p = .052$, $\eta^2 = 0.009$), but there was a significant main effect of condition ($F_{1,627} = 90.193$, $p < .001$, $\eta^2 = 0.126$). Post hoc tests revealed

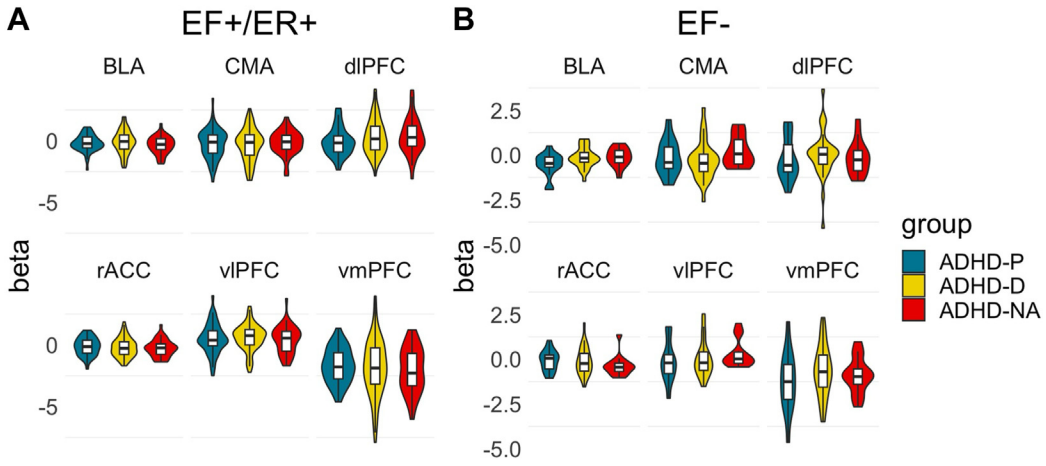


**Figure 3.** Distributions of Emotional Face n-back functional magnetic resonance imaging task blood oxygen level–dependent activations (beta) on **(A)** EF+/ER+ and **(B)** EF− trials across cortico-amygdala regions of interest separated by group. ADHD, attention-deficit/hyperactivity disorder; ADHD-D, adults with desisting ADHD symptoms; ADHD-NA, adults with no history of ADHD symptoms; ADHD-P, adults with persisting ADHD symptoms; BLA, basolateral amygdala; CMA, centromedial amygdala; dlPFC, dorsolateral prefrontal cortex; EF−, 0-back no emotional faces trials; EF+/ER+, 2-back emotional faces trials; rACC, rostral anterior cingulate cortex; vlPFC, ventrolateral PFC; vmPFC, ventromedial PFC.

that participants across groups were significantly slower on correct EF+/ER+ trials than on EF− trials ($p < .001$).

**Functional MRI.** There was no significant group-by-condition interaction effect on activation in any of the ROIs examined (*p*s ≥ .395). There was a significant main effect of group on activation in the basolateral amygdala ROI ($F_{2,1414} = 4.144$, $p = .016$, $\eta^2 = 0.006$) but no other region (*p*s ≥ .117); however, a post hoc pairwise *t* test revealed no significant between-group differences in basolateral amygdala activation (*p*s > .074). There were also significant main effects of condition on activation in the dlPFC ($F_{1,1426} = 16.675$, $p < .001$, $\eta^2 = 0.012$), vlPFC ($F_{1,1425} = 32.458$, $p < .001$, $\eta^2 = 0.022$), basolateral amygdala ($F_{1,1424} = 4.042$, $p = .045$, $\eta^2 = 0.003$), rACC ($F_{1,1427} = 11.519$, $p < .001$, $\eta^2 = 0.008$), and vmPFC ($F_{1,1431} = 66.941$, $p < .001$, $\eta^2 = 0.045$), but not in the centromedial amygdala ($p = .077$). Post hoc tests revealed significantly elevated activation across participants on EF+/ER+ trials than on EF− trials in both top-down control network ROIs: dlPFC ($p = .026$) and vlPFC ($p = .0003$). In contrast, post hoc tests revealed significantly reduced activation on EF+/ER+ trials than on EF− trials in several affective salience network regions: basolateral amygdala ($p = .012$), rACC ($p = .012$), and vmPFC ($p < .001$). See Figure 3 for distributions of fMRI blood oxygen level–dependent task activation beta values by ROI.

## Associations Between Neural Activation and EFNBACK Performance

Given our interest in understanding resistance to emotional interference, we focused our primary analyses examining the relationship between neural activation and EFNBACK performance on EF+/ER+ trials.

**Accuracy.** There were significant group-by-condition interactions on EFNBACK EF+/ER+ trial accuracy in the dlPFC ($F_{2,1066} = 10.235$, $p < .001$, $\eta^2 = 0.019$), vlPFC ($F_{2,1066} = 7.810$, $p < .001$, $\eta^2 = 0.014$), and centromedial amygdala ($F_{2,1068} = 3.909$, $p = .020$, $\eta^2 = 0.007$), but not in any other ROI (*p*s ≥ .227). Post hoc tests revealed that heightened activation in all 3 ROIs was associated with higher accuracy on EF+/ER+ trials in the ADHD-P group: dlPFC ($F_{1,277} = 21.907$, $p < .001$, $\eta^2 = 0.073$), vlPFC ($F_{1,276} = 11.805$, $p < .001$, $\eta^2 = 0.041$), and centromedial amygdala ($F_{1,276} = 6.336$, $p = .012$, $\eta^2 = 0.022$). In contrast, heightened activation in all 3 ROIs was associated with lower accuracy on EF+/ER+ trials in the ADHD-NA group: dlPFC ($F_{1,248} = 4.656$, $p = .032$, $\eta^2 = 0.018$), vlPFC ($F_{1,248} = 13.538$, $p < .001$, $\eta^2 = 0.052$), and centromedial amygdala ($F_{1,247} = 4.459$, $p = .036$, $\eta^2 = 0.018$). Finally, in contrast to both the ADHD-P and the ADHD-NA groups, neural activation in these regions was not associated with EF+/ER+ trial accuracy in the ADHD-D group: dlPFC ($F_{1,541} = 0.009$, $p = .926$), vlPFC ($F_{1,542} = 2.394$, $p = .122$), and centromedial amygdala ($F_{1,545} = 0.007$, $p = .934$). See Figure 4A for associations between ROI activation and EFNBACK EF+/ER+ accuracy by group.

**Response Times.** There were significant group-by-condition interactions on EFNBACK EF+/ER+ correct trial response times in the dlPFC ($F_{2,1066} = 8.117$, $p = .003$, $\eta^2 = 0.015$), vlPFC ($F_{2,1066} = 13.364$, $p < .001$, $\eta^2 = 0.024$), rACC ($F_{2,1068} = 11.831$, $p < .001$, $\eta^2 = 0.022$), and basolateral amygdala ($F_{2,1066} = 3.826$, $p = .022$, $\eta^2 = 0.007$), but not in the vmPFC or centromedial amygdala (*p*s ≥ .383). Post hoc tests revealed that activation in neither top-down control ROI was associated with response times in the ADHD-P group (both *p*s ≥ .202); however, heightened activation in both regions was associated with slower response times in the ADHD-D group (dlPFC: $F_{1,541} = 6.154$, $p = .013$, $\eta^2 = 0.011$; vlPFC: $F_{1,542} = 16.125$, $p < .001$, $\eta^2 = 0.029$) and ADHD-NA group (dlPFC: $F_{1,248} = 27.628$, $p < .001$, $\eta^2 = 0.10$; vlPFC: $F_{1,248} = 37.788$, $p < .001$, $\eta^2 = 0.132$). In the ADHD-P group, heightened rACC activation was associated with faster response times on correct EF+/ER+ trials ($F_{1,273} = 4.99$, $p = .026$, $\eta^2 = 0.018$), whereas heightened rACC activation was associated with

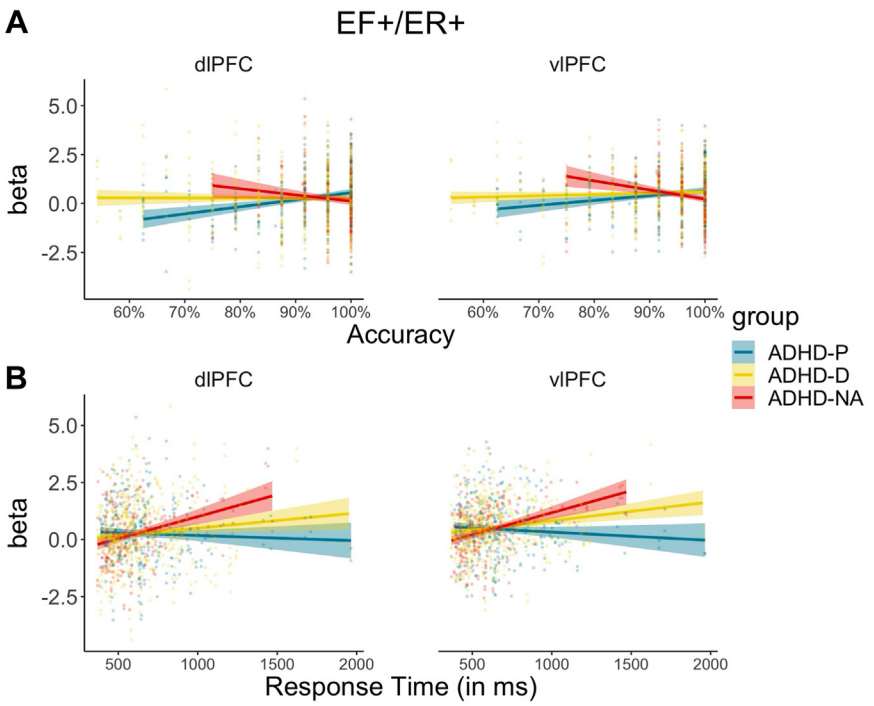


**Figure 4.** Associations between lateral prefrontal cortex blood oxygen level–dependent activation during EF+/ER+ trials and emotional face n-back **(A)** mean accuracy and **(B)** response times on correct trials for each group. ADHD, attention-deficit/hyperactivity disorder; ADHD-D, adults with desisting ADHD symptoms; ADHD-NA, adults with no history of ADHD symptoms; ADHD-P, adults with persisting ADHD symptoms; dlPFC, dorsolateral prefrontal cortex; EF+/ER+, 2-back emotional faces trials; vlPFC, ventrolateral PFC.

slower response times in both the ADHD-D ($F_{1,548}$ = 10.374, $p$ = .001, $\eta^2$ = 0.019) and the ADHD-NA ($F_{1,247}$ = 18.576, $p$ < .001, $\eta^2$ = 0.07) groups on correct EF+/ER+ trials. Basolateral amygdala activation was not associated with response times in either ADHD group (both $p$s ≥ .122), but heightened activation in this region was associated with shorter response times in the ADHD-NA group ($F_{1,248}$ = 5.321, $p$ = .020, $\eta^2$ = 0.021). See Figure 4B for associations between ROI activation and EFNBACK EF+/ER+ response times on correct trials by group.

## Associations With Affect Lability

An analysis of variance test revealed significant group differences in emotional lability ($F_{2,253}$ = 15.13, $p$ < .001). Post hoc pairwise $t$ tests revealed significantly greater emotional lability in the ADHD-P group compared with the ADHD-D group ($p$ < .001) and ADHD-NA group ($p$ < .001). However, following multiple comparisons correction, the ADHD-D group did not significantly differ in emotional lability from the ADHD-NA group ($p$ = .062). Given our interest in understanding emotional symptoms in adults with persisting ADHD symptoms, we performed analyses to test the relationship between EFNBACK performance and neural activation with affect lability in the ADHD-P group on EF+/ER+ trials.

**Behavioral.** Greater affect lability was associated with lower accuracy on EF+/ER+ trials in ADHD-P participants ($F_{1,138}$ = 14.558, $p$ < .001, $\eta^2$ = 0.095). Affect lability was not associated with response times on correct trials in the ADHD-P group ($p$ = .947) (see Table 2).

**Functional MRI.** Greater affect lability was associated with reduced activation in top-down control regions in the ADHD-P group (dlPFC: $F_{1,277}$ = 18.468, $p$ < .001, $\eta^2$ = 0.063; vlPFC: $F_{1,276}$ = 23.356, $p$ < .001, $\eta^2$ = 0.078); however, affect lability was not associated with activation in affective salience network ROIs ($p$s ≥ .442).

## Exploratory Mediation Analysis

Exploratory mediation analyses tested the extent to which activation in top-down control ROIs (i.e., dlPFC, vlPFC) during EF+/ER+ trials mediated the association between affect lability and EFNBACK accuracy. Our analysis controlled for mean scores of overall ADHD symptom severity to ensure that any detected effects were specific to emotional symptoms and not accounted for

**Table 2. Correlation Matrices for 2-Back Emotional Faces Trials in ADHD Groups**

| | | Correlation (Pearson's $r$) | | | | |
|---|---|---|---|---|---|---|
| Variable of Interest | | 1 | 2 | 3 | 4 | 5 |
| 1 | EFNBACK Accuracy | – | −0.46[a] | −0.002 | 0.01 | −0.05 |
| 2 | EFNBACK Response Time | – | – | 0.07 | 0.06 | 0.01 |
| 3 | Inattention | – | – | – | 0.76[a] | 0.38[a] |
| 4 | Impulsivity/Hyperactivity | – | – | – | – | 0.41[a] |
| 5 | Affect Lability | – | – | – | – | – |

ADHD groups were adults with persisting ADHD symptoms (ADHD-P) and adults with desisting ADHD symptoms (ADHD-D). Accuracy refers to the number of correct trials over total trials. Response time refers to time taken in milliseconds of correct trial responses. ADHD symptoms of inattention and impulsivity/hyperactivity were assessed using the Barkley Adult ADHD Rating Scale–IV, and affect lability was evaluated using the 18-item Affect Lability Scales.

ADHD, attention-deficit/hyperactivity disorder; EFNBACK, emotional face n-back (task)

[a]$p$ < .001

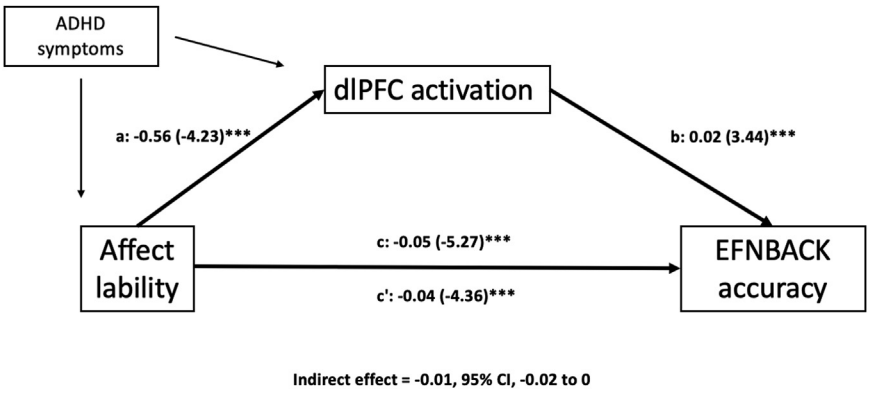


**Figure 5.** Exploratory mediation model showing dlPFC activation during EF+/ER+ trials mediating the association between affect lability and task accuracy, after controlling for ADHD symptoms in adults with persisting ADHD ($n$ = 47). The *a* path is the association between affect lability and the mediator variable (dlPFC activation). The *b* path is the association between the mediator variable and EFNBACK EF+/ER+ trial accuracy. The *c′* path is the direct effect of affect lability on EFNBACK EF+/ER+ trial accuracy. The *c* path is the total effect of affect lability on EFNBACK EF+/ER+ trial accuracy. ADHD, attention-deficit/hyperactivity disorder; dlPFC, dorsolateral prefrontal cortex; EF+/ER+, 2-back emotional faces trials; EFNBACK, emotional face n-back. ***$p < .001$.

by cognitive aspects of ADHD (e.g., inattention and/or impulsivity/hyperactivity).

We found that dlPFC activation during EF+/ER+ partially mediated the association between affect lability and EFNBACK accuracy. The results of the mediation analysis after bootstrapping revealed a significant indirect (mediating) effect of dlPFC activation during EF+/ER+ trials in the relationship between affect lability and EFNBACK accuracy (*ab*; $\beta = -0.01$, $p = .004$), with a significant proportion of the relationship mediated by the dlPFC ($\beta = 0.16$, $p = .004$). There was also a significant direct effect (*c′*; $\beta = -0.04$, $p < .001$) as well as a significant total effect (*c*; $\beta = -0.05$, $p < .001$). In sum, results indicated that affect lability had both direct and indirect effects on (associations with) EFNBACK accuracy through dlPFC activation (see Figure 5 for mediation model), above and beyond ADHD symptom severity. Critically, this test represents a statistical mediation, as causal mediation cannot be established with the present cross-sectional study design.

## DISCUSSION

Emotional symptoms are common in adults with persisting ADHD symptoms, yet their functional neuroanatomy remains poorly understood. In the present study, we used an emotional face working memory paradigm (EFNBACK) in adult participants with persisting, desisting, or no childhood or adulthood ADHD symptoms while undergoing fMRI scanning. Findings show that reduced activations in the dlPFC and vlPFC during high cognitive load (2-back) and emotional distractors (trials with faces) in adults with persisting ADHD symptoms were associated with more severe affect lability. This association remained significant even after accounting for variability in inattention and impulsivity/hyperactivity symptoms within the ADHD-P group, suggesting that emotional symptoms may correlate with additional behavioral and neural variability. Mediation analyses further showed that dlPFC activation during EF+/ER+ trials in the ADHD-P group statistically mediated the association between affect lability and performance (task accuracy), above and beyond ADHD symptoms. Taken together, our results implicate the dlPFC—a cortical structure involved in attention selection and cognitive control—in emotional dysregulation in adults with persisting ADHD, such as in affect lability.

Our findings largely support our main hypothesis: As expected, less activation in lateral PFC regions was associated with more emotionality (e.g., affect lability); however, we did not observe a positive relationship between activation in affective salience structures (e.g., the amygdala or vmPFC) and affect lability as we had expected. In addition, although greater activation in the dlPFC and vlPFC was associated with better performance on EF+/ER+ EFNBACK trials, this association was present only in the ADHD-P group. Surprisingly, stronger vlPFC activation was associated with worse performance in the ADHD-NA group, suggesting that the structure may differentially relate to behavioral performance on a cognitive task in adults with versus without ADHD.

Previous research using the EFNBACK task has documented similar working memory deficits in adults with ADHD compared with adults without ADHD, along with more pronounced difficulties with emotional interference control in the former group relative to the latter (12). Earlier research has implicated the ACC in adults with ADHD when viewing negative versus neutral images (46); however, this work contrasted negative and neutral pictures to test emotional processing and regulation, to which our results cannot directly speak. A large body of evidence also implicates the amygdala and vlPFC in working memory performance when facing emotional interference (33,29), which is not necessarily at odds with our findings: Although our fMRI task included emotional faces, our study design did not include subjective measures of distractibility or eye movement indices of distraction, thereby precluding any conclusion that participants experienced the distracting stimuli as salient or emotionally evocative.

Our results differ from previous work that has used the EFNBACK fMRI task in adults with and without ADHD. Albeit with fewer participants, the study investigators failed to observe a significant difference in dlPFC activation between adults with and without ADHD (47). The authors of that study attributed the lack of group difference in dlPFC (and amygdala) activation to the fact that they recruited adult participants, suggesting that symptoms conferring functional impairment present during childhood and into adolescence may no longer be present in older participants. Our study extends this work by recruiting and differentiating adults with persisting from desisting ADHD symptoms at the time of assessment, which

may explain some of the discrepancies in findings. Indeed, our results are consistent with previous work performed in younger participants, which has shown dlPFC differences in structure (48) and function (49) in emotional symptoms in participants with ADHD relative to typically developing youth.

Interestingly, heightened activation in the dlPFC and vlPFC during EF+/ER+ EFNBACK trials was associated with more accurate performance on these trials, but only in the ADHD-P group. We interpret these findings to suggest that successful lateral PFC recruitment and engagement in adults with persisting ADHD symptoms may be associated with greater emotional interference resistance. This is consistent with our result showing that greater engagement of the dlPFC/vlPFC in adults with persisting ADHD symptoms was associated with less affect lability.

Recent evidence has suggested a complex dynamic between cognitive and affective processes in ADHD, with some suggesting that deficits in working memory and attentional control may contribute directly and indirectly to symptoms characterized by emotion dysregulation (50,51). Researchers investigating emotion regulatory strategies reported that individuals with ADHD may be employing more emotional suppression as a compensatory approach to manage emotionality rather than cognitive reappraisal (52), with the latter being more effective in reducing negative affect relative to the former linked with heightened physiological response (53). Given that current conceptualizations of emotional interference resistance underscore lateral PFC structures (31,32), it is plausible that functional impairment of these neural structures contributes to heightened emotionality (e.g., lability) in ADHD, possibly due to less successful cognitive reappraisal. However, because the present study did not explicitly elicit emotional states or test regulatory strategies, this too would require explicit testing in adults with varying levels of symptom persistence as well as with heterogeneous affective and cognitive control in varying contexts. See the Supplemental Discussion, including strengths and limitations.

## Conclusions

Findings from this study add to the sparse literature on the neural underpinnings of voluntary emotion regulation linked to emotional symptoms in adults with childhood-onset ADHD. Because the adults in our samples were diagnosed in childhood and followed through adulthood, it was possible to examine whether ADHD symptom persistence is associated with alterations in the functioning of emotion regulation circuitry and emotional symptoms of ADHD. Our findings identify reduced functional activation in lateral cortical structures (i.e., dlPFC, vlPFC) as likely contributors to the pathoetiology of ADHD symptoms related to affective control. Given emerging evidence indicating promising results for cognitive symptoms of ADHD when targeting the lateral PFC (e.g., using pharmacological or neuromodulatory approaches), we encourage future investigators to consider measuring changes in the severity of emotional symptoms in adults with ADHD when carrying out such experiments.

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