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Executive Functioning Moderates Neural Mechanisms of Irritability During Reward Processing in Youth: Preliminary Findings

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in

Clinical Psychology

by

Maria Emilia Kryza-Lacombe

Committee in charge:

San Diego State University

Professor Jillian Lee Wiggins, Chair
Professor Vanessa Robin Weersing

University of California San Diego

Professor Natacha Akshoomoff
Professor Lisa T. Eyler
Professor Charles T. Taylor

2022

The dissertation of Maria Emilia Kryza-Lacombe is approved, and it is acceptable in quality and form for publication on microfilm and electronically.

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Chair

University of California San Diego

San Diego State University

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VITA

2009 Bachelor of Science in Psychology, State University of New York, Plattsburgh

2016 Master of Arts in General Psychology, City College of New York

2018 Master of Science in Clinical Psychology, San Diego State University

2022 Doctor of Philosophy in Clinical Psychology, University of California San Diego and San Diego State University

ABSTRACT OF THE DISSERTATION

Executive Functioning Moderates Neural Mechanisms of Irritability During Reward Processing in Youth: Preliminary Findings

by

Maria Emilia Kryza-Lacombe

Doctor of Philosophy in Clinical Psychology

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San Diego State University, 2022

Professor Jillian Lee Wiggins, Chair

Rationale. Irritability is highly impairing and prevalent in pediatric psychopathology and typical development, yet underlying mechanisms and ameliorating factors are largely unknown. Irritability is associated with altered neural reward processing, including neural networks related to cognitive control, and better cognitive control has been hypothesized to mitigate irritability. To test this hypothesis, this study evaluated the relationship of executive functioning (EF; a

measurable form of cognitive control) with irritability-related neural correlates of reward processing in youths with varying levels of irritability.

Design. An archival dataset of 51 youths with a history of or at risk for mood disorders was used (age range = 9-19; mean age = 13.80 years, SD = 1.94). Irritability and EF were measured via the Affective Reactivity Index and the NIH Toolbox, respectively. Neural reward processing was measured via a monetary incentive delay task during fMRI acquisition: participants "hit" a target to obtain a potential reward. Neural activation across the entire brain, and ventral striatum (VS) and amygdala connectivity with the rest of the brain, were measured during reward anticipation and performance feedback. Multivariate general linear models, controlling for age, examined whether EF moderates the relationship between irritability and neural reward processing, separately for anticipation and performance feedback.

Results. EF moderated irritability-related neural patterns during anticipation and performance feedback. In some brain areas/networks (VS-cuneus connectivity during anticipation; limbic activation and amygdala-temporal connectivity during performance feedback) differences were found regardless of task conditions: the combination of higher irritability and lower EF was associated with hyperactivation and hypoconnectivity, whereas the combination of higher irritability and higher EF was associated with the opposite pattern. In other areas/networks (cuneus activation during anticipation; frontal, limbic, temporal activation, and right VS-frontal connectivity during performance feedback), neural patterns depended on task condition and were generally opposite for higher irritability combined with lower EF versus higher irritability combined with higher EF.

Conclusions and Implications. This study is a step toward understanding the interaction of top-down EF processes in pediatric irritability, which provides the necessary groundwork to build mechanistic interventions.

CHAPTER 1: INTRODUCTION

Irritability, defined as a greater tendency, relative to peers, to anger and frustration in response to blocked goals (Brotman et al., 2017), is the most common self- and parent-reported symptom among youths (Collishaw et al., 2010) and one of the most common reasons parents seek psychiatric care for their children (Peterson et al., 1996). Elevated irritability manifests in many pediatric psychiatric disorders, including mood and disruptive behavior disorders (Stringaris, 2011; Wakschlag et al., 2018). Pediatric irritability symptoms relate to worse concurrent (Stringaris, Zavos, et al., 2012; Wiggins et al., 2018) and future (Dougherty et al., 2017; Savage et al., 2015; Stringaris et al., 2009; Wiggins et al., 2021) impairment and mental health, greater propensity for maladaptive coping (Tarter et al., 1995), poorer academic performance (Pekrun et al., 2017), and reduced educational and socioeconomic attainment (Stringaris et al., 2009). Despite irritability's transdiagnostic import, little is known about mechanisms that may play an ameliorating or aggravating role in its development and maintenance, hampering efforts to generate much-needed mechanism-driven interventions (Kircanski et al., 2018).

Altered reward processing has been suggested as a candidate mechanism of irritability in youths (Brotman et al., 2017). Indeed, youths with elevated irritability may assign greater salience to rewards (Bebko et al., 2014; Kessel et al., 2016; Perlman et al., 2015) and have more difficulty adjusting to changing reward contingencies (Deveney et al., 2013) – a combination that leads to a more intense experience of frustration when desired outcomes fail to materialize, i.e., prediction error (Tseng et al., 2019). Indeed, our prior work suggests that reward processing mechanisms leading to irritability may include aberrant processes in anticipation of and in response to reward: Using a monetary incentive delay task, we found that higher vs. lower

irritability levels were associated with increased striatal activation and decreased limbic-prefrontal connectivity regardless of task condition during both reward anticipation and feedback on whether they successfully obtained or failed to obtain a reward (Kryza-Lacombe et al., 2021). In addition, we (Kryza-Lacombe et al., 2021) and others (Adleman et al., 2011; Deveney et al., 2013; Dougherty et al., 2018; Perlman et al., 2015; Yu et al., 2014), documented a pattern of more pronounced neural activation and connectivity differences between task conditions (e.g., reward vs. no reward) in distributed prefrontal, amygdala, and striatal networks in youths with higher vs. lower irritability. Interestingly, alterations in frontal and limbic-frontal networks in addition to reward regions in these reward tasks are almost ubiquitous – suggesting a common thread of cognitive control deficits in addition to the reward dysfunction.

Executive functioning is a measurable form of cognitive control, is important for effective anger modulation (Carlson, 2007; Perlman et al., 2010), and has been conceptualized as a multicomponent system. It includes cognitive flexibility, which allows for changing perspectives or approaches to a problem and flexible adjustment to new demands, rules, or priorities, and inhibitory control, which is the ability to control one's attention, behavior, thoughts, and emotions to override an internal drive or external pull (Diamond, 2013). Although conceptually distinct, these aspects of executive functioning are highly correlated (Akshoomoff et al., 2018) and subserved by overlapping frontal and parietal neural networks (Niendam et al., 2012). Developmentally, these executive functioning components follow a non-linear trajectory characterized by rapid gains before age 10 and slower, more gradual gains thereafter (Akshoomoff et al., 2014). Importantly, cognitive flexibility and inhibitory control build on each other developmentally (Dajani et al., 2015) and load onto a common executive functioning factor as early as age 7 (Akshoomoff et al., 2018; Miyake et al., 2012). Furthermore, we recently

demonstrated that a composite measure of these two aspects of executive functioning moderates neural reward processing (Kryza-Lacombe et al., 2020).

Executive functioning deficits may exacerbate aberrant reward processing (Kircanski et al., 2019), and this may be especially pertinent in adolescence as neural networks related to executive functioning and reward processing networks undergo rapid yet disjointed changes during this developmental period (Somerville et al., 2010): striatal (Galvan, 2014), and amygdala (Ernst, 2014; Richards et al., 2012) circuitry, key circuits involved in reward processing, show dramatic maturational gains in early adolescence (Somerville et al., 2010). In contrasts, the prefrontal cortex, which plays a key role in cognitive control, shows a delayed and protracted maturation (Hsu et al., 2014) and is not fully developed until the early 20s (Cohen et al., 2016; Geier, 2013). Theoretical models of the development of neural networks in childhood (see (Shulman et al., 2016) for an overview) posit that more mature executive functioning networks may dampen an overactive reward-system and thereby promote adaptive functioning. This hypothesis is consonant with our recent evidence that youths with better executive functioning evince less pronounced neural activation and connectivity differences when exposed to varying reward conditions compared with youths with worse executive functioning who demonstrate exaggerated neural fluctuations between reward conditions (Kryza-Lacombe et al., 2020).

Previous research suggests that deficits in executive functioning play a role in youth irritability, including by ameliorating aberrant reward processing. For example, on a behavioral level, children with better inhibitory control more effectively modulate anger when waiting for an expected reward (Cole et al., 2011). At the neural level, adolescents with higher levels of irritability demonstrate greater prefrontal activation during response inhibition (Fishburn et al., 2019; Li et al., 2017; Liuzzi et al., 2020) and attention orienting following frustration (Tseng et

al., 2019). Furthermore, event-related potentials research demonstrated that high executive functioning is related to greater conflict monitoring when children engage in an inhibitory control task while frustrated (Deveney et al., 2018).

Overall, despite burgeoning literature documenting the involvement of neural networks related to both reward processing and executive functioning in irritability, no work has examined whether executive functioning moderates reward-related deficits in youth irritability. Compensatory cognitive control processes may mitigate reward processing deficits and lessen ensuing irritability symptoms or, conversely, poor executive functioning may worsen reward processing deficits and produce greater irritability. To address these gaps in the literature, the present study explored the potential moderating effect of executive functioning (measured behaviorally) on irritability-related differences in neural reward processing during reward anticipation and performance feedback via conservative whole-brain activation and connectivity analyses. Irritability was conceptualized as a dimensional construct in line with Research Domain Criteria efforts that have promoted a dimensional perspective to evaluate the neural underpinnings of symptom dimensions (Morris et al., 2012).

Building on theoretical frameworks positing that better executive functioning dampens overactive reward processing (Shulman et al., 2016) as well as evidence that worse executive functioning (Kryza-Lacombe et al., 2020) and greater irritability (Kryza-Lacombe et al., 2021) are associated with more pronounced differences in neural response between reward task conditions, we broadly expected that better relative to worse executive functioning would be associated with less pronounced irritability-related activation and connectivity differences between task conditions in distributed frontal and limbic networks. Additionally, given our previous work demonstrating that higher irritability was associated with increased striatal

activation and decreased limbic-prefrontal connectivity regardless of task condition during both reward anticipation and performance feedback (Kryza-Lacombe et al., 2021), we expected that better executive functioning would attenuate the striatal hyperactivation and limbic-prefrontal hypoconnectivity associated with higher levels of irritability.

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CHAPTER 2: METHOD

Participants

Data from 51 youths (mean age=13.80 years, *SD*=1.94) were included. To enrich for irritability, participants were recruited from intervention-seeking families at local research clinics. Table 1 lists participant characteristics. See Appendix for details about recruitment sources and Table S1 for subsample characteristics. Data collection procedures were identical across recruitment sources and subsamples did not differ in gender distribution ($\chi^2[2] = .10$, $p = .95$), irritability ($F_{2,48} = .18$, $p = .84$), executive functioning ($F_{2,48} = 1.33$, $p = .28$), anxiety ($F_{2,48} = .54$, $p = .57$), or depression levels ($F_{2,45} = 1.82$, $p = .17$). Subsamples differed in mean age ($F_{2,48} = 15.73$, $p < .01$) despite highly overlapping age ranges (subsample 1 [n=33]: 11.04-15.05 years; subsample 2 [n=14]: 12.39-19.44 years; subsample 3 [n=4]: 9.69-14.97 years). Age was added as a covariate across all statistical models. As a subset (n=11) was taking psychotropic medication and samples differed in externalizing symptoms ($F_{2,35} = 6.74$, $p < .01$), post-hoc analyses evaluated the potential impact of those variables on the results.

Exclusion criteria included MRI contraindications (e.g., orthodontic braces) and presence of a major co-occurring neurological disorder. Parental permission and child assent were obtained for participants under 18, and participants aged 18 and above provided written informed consent. The University of California San Diego Institutional Review Board, in joint agreement with the San Diego State University Institutional Review Board, approved all procedures.

Data from subsets of participants in the present sample have been used in prior work to answer different research questions (Maria Kryza-Lacombe et al., 2020; Kryza-Lacombe et al., 2021; M. Kryza-Lacombe et al., 2020; Liuzzi et al., 2020; Schwartz et al., 2019).

Youth Irritability

Irritability was measured via the parent- and youth-reported Affective Reactivity Index (ARI, 6-month version), a well-validated measure with good psychometric properties (parent-report α=0.92, child-report: α=0.89) (Stringaris, Goodman, et al., 2012). This six-item irritability symptom measure includes probes (e.g., "loses temper easily," "stays angry for a long time") rated as 0 (not true), 1 (sometimes true), or 2 (certainly true), with total scores ranging from a possible 0-12. The present sample was enriched for clinical diagnoses associated with irritability (i.e., depression and/or anxiety) and exhibited substantial variability in irritability (parent-report: *M*=1.87; *SD*=2.19; child self-report: *M*=2.38; *SD*=2.37). This included higher ranges of the irritability spectrum, similar to "at risk" youths described in previous work (Stringaris, Goodman, et al., 2012). Scores from parent- and child-report were averaged, to maintain continuity with our previous study (Kryza-Lacombe et al., 2021), and other studies investigating irritability-related neural mechanisms (Stoddard et al., 2017; Tseng et al., 2019; Wiggins et al., 2016), upon which the present analyses build. Supplemental analyses evaluated parent- and youth-reported irritability separately (see Supplementary Tables S5-6). Additional symptom measures used to evaluate potential confounding factors (i.e., depression, anxiety, externalizing symptoms), are described in Appendix.

Executive Functioning Tasks

In the present study, executive functioning was defined as performance on two standardized tasks from the NIH Toolbox cognitive battery (Bauer et al., 2014) that measured two aspects of executive functioning: the Dimensional Change Card Sort and a Flanker task assessed cognitive flexibility and inhibitory control, respectively. Participants completed these tasks on an iPad outside the scanner on the same day as the fMRI scan. Both tasks have been

validated for use in children and adults, and show excellent reliability and convergent validity (Zelazo et al., 2013). As performance on the two tasks is highly correlated (in this sample, r=0.67) and because cognitive flexibility and inhibitory control load on the same general executive functioning factor in youths ages 7-21 (Akshoomoff et al., 2018), a composite executive functioning score was created by averaging the uncorrected standard scores, as in prior work (Maria Kryza-Lacombe et al., 2020). Secondary analyses examined cognitive flexibility and inhibitory control separately (see Supplementary Tables S7-8). Additional details about the tasks and score calculation are presented in Appendix.

Child-friendly Monetary Incentive Delay Task

Participants completed a task during fMRI acquisition, in which they tried to hit a pinata to win stars which they would later exchange for money. This task captures neural correlates of reward processing during reward anticipation and performance feedback (including reward omission and receipt) and reliably elicits reward-related brain activation in children, including in the striatum, thalamus, insula, and prefrontal cortex (Dougherty et al., 2018; Helfinstein et al., 2013; Maria Kryza-Lacombe et al., 2020; Kryza-Lacombe et al., 2021; Wiggins et al., 2017). Each trial began with an anticipation period in which the participant saw a cue (pinata with or without stars) indicating whether there was a potential reward or not in that trial (2000ms), followed by a jittered delay (2500-5500ms). Then, the participants were presented with a target (i.e., piñata) which they were instructed to "hit" by pressing a button. Participants were instructed to attempt to "hit" the piñata regardless of reward condition. Time to hit the piñata was initially 500ms but automatically adjusted in real time (+/-50ms), based on performance, to maintain an approximate 2/3 hit rate; total target duration plus a delay was 1500ms. If the participant pressed the button within the allotted time, the piñata broke and stars fell out,

indicating a hit; missed targets swung away (1500ms). Finally, a basket was displayed showing the stars won (or no stars) (1500ms). There were four possible performance feedback scenarios: 1) reward/hit, 2) reward/miss, 3) no reward/hit, 4) no reward/miss. Inter-trial intervals were jittered. Participants completed three runs, approximately 5 minutes each, with a total of 60 trials across all runs (30 reward, 30 no reward).

Neuroimaging Acquisition

A General Electric 3T MR750 Discovery MRI scanner and Nova Medical 32-channel head coil were used to acquire anatomical and functional brain images. Multiband procedures increased spatial and temporal resolution, thus allowing for improved inference of irritability correlates. A 2D multiband EPI pulse sequence acquired T2* blood oxygen level dependent (BOLD) images across 3 runs as 60 interleaved axial slices approximately parallel to the AC-PC line, with whole-brain coverage (voxel size=2x2x2mm, 370 image volumes per run, matrix size=104x104, multiband acceleration factor=6, TR=800ms, TE=29ms, flip angle=52°, FOV=20.8mm). High-resolution anatomical images with prospective motion correction (PROMO; T1-weighted 3D MPRAGE) were acquired for anatomical localization and spatial normalization (sagittal scan plane, locs per slab=256, flip angle=8°, matrix size=256x256, FOV=25.6mm, voxel size=1x1x1mm). Task stimuli were projected onto a screen at the foot of the MRI bed and seen by the participant via a mirror attached to the head coil. Participants used a 2-button response box to "hit" the piñata using their dominant hand.

fMRI Data Preprocessing

Analysis of Functional NeuroImages (AFNI; https://afni.nimh.nih.gov/afni/) preprocessing protocols were implemented and included slice-time correction, functional image realignment, EPI/anatomical registration, and non-linear registration to the Talairach template

(all spatial transformations of EPI data were concatenated and applied as one to avoid multiple interpolations), followed by 4mm spatial smoothing and voxelwise scaling into units of percent signal change. Image volume pairs with frame-wise displacement >1mm were censored from individual level analysis. Mean frame-wise displacement (head motion) was ≤0.15mm across all participants.

fMRI Data Analysis

First-level models. In addition to the regressors of interest described below, all first-level models included head motion in x, y, z, roll, pitch, yaw directions and third-degree polynomials to model low-frequency drift as nuisance regressors.

Activation. Individual-level general linear models generated estimates of brain activation during anticipation and feedback periods. For the anticipation period, the regressor of interest (Reward Condition [reward, no reward]) was convolved with AFNI's 'dmBLOCK' basis function over variable duration. The regressors of interest for the feedback period included Reward Condition (reward, no reward) and Performance (hit, miss), and were both convolved with the 'BLOCK' function over 4500ms. Analyses generated beta coefficients at each voxel for each condition (anticipation period: reward, no reward; feedback period: reward/hit, reward/miss, no reward/hit, and no reward/miss).

Connectivity. Generalized psychophysiological interaction analysis (gPPI) (McLaren et al., 2012) was used to calculate functional connectivity during reward anticipation and feedback for each individual. The amygdalae and ventral striatum (nucleus accumbens) were utilized as seeds for gPPI analyses based on our previous work (Maria Kryza-Lacombe et al., 2020; Kryza-Lacombe et al., 2021) and given prior fMRI studies relating reward and irritability (Deveney et al., 2013; Dougherty et al., 2018; Perlman et al., 2015). Seed regions were identified using the

Talairach atlas in AFNI (left amygdala=1288mm^3; right amygdala=1280mm^3; left ventral striatum=136mm^3; right ventral striatum=168mm^3). These analyses resulted in voxel-wise images representing connectivity between each seed region and the rest of the brain, for each condition.

Second-level models. Whole-brain, group-level repeated-measures ANCOVAs using AFNI's 3dMVM program evaluated executive functioning as a moderator of the relationship between irritability and reward-related brain function. Models were run separately for activation and connectivity as well as for reward anticipation and feedback periods. Analyses tested the interaction of executive functioning and irritability, depending on task conditions, using an omnibus model (including lower-level interactions). Contrasts (i.e., interactions) of interest (Table 2) examined brain patterns regardless of task condition (i.e., Executive Functioning x Irritability) as well as brain patterns that depended on task condition (i.e., for both reward anticipation and performance feedback: Executive Functioning x Irritability x Reward Condition; for performance feedback only: Executive Functioning x Irritability x Performance, Executive Functioning x Irritability x Reward Condition x Performance). Examining brain patterns regardless of task condition identifies mechanisms linked to the reward processing phase (i.e., anticipation; performance feedback) that do not depend on specific circumstances (i.e., reward vs. no reward and/or hit vs. miss conditions). Examining brain patterns depending on task conditions identifies mechanisms that vary by specific circumstances (i.e., reward vs. no reward and/or hit vs. miss conditions) during reach reward processing phase.

Analyses were conducted separately for whole-brain activation and for each seed of interest for connectivity. Age was added as a covariate across all analyses to control for developmental changes related to brain functioning, irritability, and executive functioning. Due

to limited power in the present sample, age interactions with the variables of interest were not examined. Additional secondary analyses separately examined the moderating role of cognitive flexibility and inhibitory control in relation to reward-processing-related irritability neural mechanisms (see Supplementary Tables S7-8).

In line with the most recent recommendations (Cox, 2017), the mixed-model spatial autocorrelation function (-acf) and the NN1 2-sided option as calculated by AFNI's 3dClustSim were used to determine a whole-brain corrected cluster threshold of α=.05 (cluster height threshold was set at p<.005, extent threshold k≥60 voxels). Model parameter estimates were averaged over runs for each participant, and then averaged across participants. Beta coefficients of each voxel from resulting clusters in each analysis were averaged and extracted to illustrate significant omnibus findings for the interactions of interest. Extracted data were also examined for outliers (defined as 3 standard deviations away from median for one or more conditions), and models were rebuilt in SPSS and rerun without the potential outlier. Additionally, we assessed the potential impact of other factors on our main findings by examining whether the relevant interactions of interest were still significant after covarying for anxiety, depression, and externalizing symptoms, ethnicity, race, psychotropic mediation use, residual motion, and recruitment source.

Clusters that emerged in supplemental analyses examining parent- and child-rated irritability separately, as well as inhibitory control and cognitive flexibility separately, are listed in Supplemental tables S5-6 and S7-8, respectively.

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CHAPTER 3: RESULTS

Behavioral Findings

There was no behavioral association between irritability and executive functioning, controlling for age (r_p=-.21, p=.15). Associations between variables of interest in the present analyses (irritability, executive functioning) and demographic and clinical characteristic are presented in Supplemental Table S2. In summary, there were no significant associations among variables, except for a significant correlation between irritability and externalizing symptoms (r=.49, p<.01).

fMRI Results

Table 3 summarizes main findings across analyses. The interactions of interest for which significant clusters emerged are described below. Additional findings (e.g., task effects, age effects) are listed in Supplemental Tables S3-4.

Reward anticipation.

Activation.

Executive Functioning x Irritability x Reward Condition (Figure 1A). A significant cluster emerged in the right cuneus. Youths with higher levels of irritability drove the interaction. Specifically, during reward trials, youths with higher irritability combined with higher executive functioning showed greater activation than those with higher irritability combined with lower executive functioning. In contrast, during no-reward trials, the pattern was the opposite – greater activation was seen in youths with higher irritability combined with higher executive functioning but less activation in youths with higher irritability combined with lower executive functioning. By contrast, youths with lower levels of irritability showed little difference in activation,

regardless of whether they had higher or lower levels of executive functioning and regardless of reward condition.

Ventral striatum connectivity.

Executive Functioning x Irritability (Figure 1B). Higher irritability combined with lower executive functioning was related to greater ventral striatum connectivity with the cuneus bilaterally, across conditions, relative to higher irritability combined with higher executive functioning. In contrast, lower levels of irritability combined with lower executive functioning was associated with less ventral striatum connectivity with the cuneus relative to lower irritability combined with higher executive functioning.

Amygdala connectivity. No amygdala connectivity clusters emerged in contrasts of interest during the anticipation period.

Performance feedback.

Activation.

Executive Functioning x Irritability (Figure 2A). Higher levels of irritability were associated with increased activation in the left amygdala/uncus, right putamen, and left the cingulate cortex, across reward and performance conditions, but only when youths also had lower executive functioning. Youths with higher levels of irritability combined with higher executive functioning exhibited less activation in those regions. Youths with lower levels of irritability combined with lower executive functioning evinced less activation compared to youths with lower irritability combined with higher executive functioning.

Executive Functioning x Irritability x Reward Condition (Figure 2B). During the reward condition, higher irritability was associated with less left inferior frontal gyrus activation when executive functioning was lower, but more activation when executive functioning was higher.

Whereas among youths with lower irritability, lower executive functioning was associated with more activation in this region compared to youths with lower irritability combined with higher executive functioning. During the no reward condition, there was increased activation among youths with higher irritability combined with lower executive functioning compared to youths with higher irritability combined with higher executive functioning. There was little difference in activation levels in this region among youths with lower irritability combined with lower vs. higher executive functioning. Similar patterns were observed for activation in the left middle temporal and fusiform gyri.

Executive Functioning x Irritability x Performance (Figure 2C). This interaction was driven by trials where the participant missed (rather than hit) the target, such that youths with higher levels of irritability combined with lower executive functioning showed greater activation in the left anterior cingulate cortex compared to youths with high irritability combined with higher executive functioning. The pattern was opposite among youths with lower levels of irritability, i.e., lower vs. higher executive functioning was associated with decreased activation.

In the right thalamus, youths also mostly differed during misses rather than hits. However, here youths with higher irritability combined with lower executive functioning had decreased activation compared to youth with higher irritability combined with higher executive functioning, and the pattern was opposite among youths with lower irritability and lower vs. higher executive functioning.

Executive Functioning x Irritability x Reward Condition x Performance (Figure 2D).

Executive functioning moderated the relationship between irritability and brain activation depending on reward condition and performance outcome (hit vs. miss) in the left precentral gyrus; this was driven primarily by trials in which youths miss the target. Greater levels of

irritability combined with lower executive functioning, compared to high irritability combined with higher executive functioning or lower levels of irritability, were associated with increased activation when missing the target during the reward condition and decreased activation when missing the target during the no- reward condition.

Ventral striatum connectivity.

Executive Functioning x Irritability x Performance (Figure 3A). When the target was missed, greater compared to lower levels of irritability were associated with less right ventral striatum connectivity with the right middle frontal gyrus but only with concurrent lower executive functioning; the pattern was the opposite for irritability combined with higher executive functioning. During hits these pattens were opposite and less pronounced.

Amygdala connectivity.

Executive Functioning x Irritability (Figure 3B). Greater levels of irritability were associated with greater left amygdala connectivity with the right inferior temporal gyrus, across task conditions, among youths with lower executive functioning, but with less connectivity among youths with higher executive functioning.

Additional analyses.

Additional analyses evaluated potentially outlier driven clusters as well as potential confounding factors. Results remained significant when potential outliers were removed, except for two clusters indicated in Table S4, which were removed from further analysis. Additionally, for every cluster, the interactions of interest remained significant, after covarying for anxiety, depression, and externalizing symptoms, ethnicity, race, psychotropic mediation use, residual motion, and recruitment source, suggesting that our findings were not primarily driven by these potentially confounding factors.

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CHAPTER 4: DISCUSSION

Building on theoretical (Brotman et al., 2017) and empirical (Dougherty et al., 2018; Kryza-Lacombe et al., 2021; Perlman et al., 2015) work that linked heightened irritability with altered reward processing as well as burgeoning work suggesting that executive functioning may additionally be involved (Cole et al., 2011; Fishburn et al., 2019; Li et al., 2017; Liuzzi et al., 2020; Tseng et al., 2019), the present study provides neuroimaging evidence documenting that reward-related neural alterations associated with irritability depend on levels of executive functioning. Overall, our findings demonstrate opposite and attenuated irritability-related neural reward processing patterns when executive functioning levels are higher vs. lower. This may suggest that better executive functioning could act as a buffer for irritability-related reward processing deficits. Yet, the opposite patterns observed for higher vs. lower executive functioning among higher levels of irritability, may likewise be linked to unique irritability-maintaining mechanisms and suggest an alternative path toward irritability generation and maintenance.

The neural networks that emerged are consistent with prior work examining irritability-related neural mechanisms in the context of reward processing (Dougherty et al., 2018; Kryza-Lacombe et al., 2021; Perlman et al., 2015) and executive functioning (Liuzzi et al., 2020; Tseng et al., 2019). Broadly, the observed patterns suggest that executive functioning skills may affect how highly irritable youths respond in situations that involve potential rewards. Higher irritability combined with lower executive functioning demonstrated patterns similar to those seen among highly irritable youths in our previous work that looked at reward processing mechanisms without taking executive functioning into consideration (Kryza-Lacombe et al., 2021). Lower executive functioning may thus be associated with over-responsivity when irritable

youths are presented with varying reward contingencies whereas better executive functioning may act as a "protective factor" against greater reward responsivity. Thus, vulnerabilities in reward processing that lead to and/or maintain irritability may be ameliorated by better executive functioning, which may eventually lead better long-term outcomes. These findings align with theoretical models of neural network development which have suggested that more mature executive functioning networks may dampen an overactive reward-system (Shulman et al., 2016) as well as behavioral work suggesting that executive functioning is involved in anger modulation (Cole et al., 2011). It is possible that highly irritable youths with better executive functioning may employ more effective emotion regulation strategies. Indeed, previous work showed an association between cognitive flexibility-related neural activation and irritability, suggesting that executive functioning and emotion regulation may share neural circuitry (Li et al., 2017). This is furthermore supported by studies showing that age-related gains in cognitive control correspond with gains in emotion regulatory capacities across adolescence that allow youth to more effectively modulate negative affect, such as frustration (Casey et al., 2008; Luciana, 2013).

Indeed, the limbic, frontal, and temporal networks that emerged during performance feedback in the present study overlap with emotion regulation networks (Pozzi et al., 2021). For example, we found that better executive functioning attenuated irritability-related hyperactivation in limbic areas (putamen, uncus/amygdala, cingulate gyrus) across task conditions during performance feedback. This was an expected finding given our previous findings demonstrating striatal hyperactivation among youths with higher levels of irritability (Kryza-Lacombe et al., 2021). Additionally, we found that frontal, temporal, and thalamic activation, as well as ventral striatum connectivity with the prefrontal cortex, differed with respect to irritability and executive functioning depending on task conditions, suggesting that

executive functioning affects how irritable youths adjust to varying reward outcomes (i.e., learning that sometimes rewards are obtained and other times they are missed).

During reward anticipation, occipital networks emerged as sites of an inter-relationship of executive functioning and irritability. Specifically, cuneus activation and ventral striatum connectivity with the cuneus differed by executive functioning and irritability. This was evident across reward conditions for cuneus activation but depended on reward condition for ventral striatum connectivity with the cuneus. Although the occipital cortex is primarily linked to visual processing, occipital findings in the context of reward anticipation are aligned with previous work demonstrating its involvement in reward anticipation (Hangya et al., 2015; Shuler et al., 2006). Changes in occipital networks have been documented to vary by irritability (Kryza-Lacombe et al., 2021; Tseng et al., 2019) and executive functioning performance (Maria Kryza-Lacombe et al., 2020) and are in line with evidence of occipital involvement in goal-directed and stimulus driven attention (Corbetta et al., 2002). Attention-related processes, which are foundational to executive functioning (Dajani et al., 2015), may thus be particularly relevant during reward anticipation – higher executive functioning may facilitate adaptive distribution of attentional resources when a potential reward presents itself.

It is important to note that although higher executive functioning appears to attenuate irritability-related neural reward processing aberrations, it is unclear whether this represents a "normalization" of functioning. The opposite patterns observed for higher vs. lower executive functioning among higher levels of irritability, may be linked to unique irritability-maintaining mechanisms and suggest an alternative path toward irritability generation and maintenance. These individual differences in irritability mechanisms have important implications for personalization of interventions. Irritable youths who present with low executive functioning

performance for their age, may benefit from interventions that promote executive functioning development, whereas those who present with more mature executive functioning skills may have other unique intervention needs. For example, aberrant threat processing is another mechanism that has been proposed to underlie irritability generation and maintenance (Brotman et al., 2017) and may play a more significant role among more irritable youths with higher executive functioning. Such individual differences have important clinical implication given previous research that demonstrated better treatment outcomes when treatment approaches are personalized (Storch et al., 2021) and modular (Evans et al., 2020).

Given the transdiagnostic nature of irritability, it will be important to disentangle how the neural reward processing patterns observed in the present study relate to other symptom dimensions. Indeed, neural alterations in the context of reward processing have also been documented in youths with depression (Forbes et al., 2009; Keren et al., 2018), anxiety (Benson et al., 2015), disruptive behaviors (Alegria et al., 2016), and attention deficit hyperactivity disorder (Plichta et al., 2014) in similar striatal and prefrontal areas as in irritability (Kryza-Lacombe et al., 2021), although sometimes with different directionality (Forbes et al., 2009). Executive functioning and irritability may interact with these symptom dimensions in unique ways and may have implications for mental health during childhood as well as psychiatric course in adulthood. Studies with larger transdiagnostic samples that are followed longitudinally are needed to answer these questions.

Notably, we did not observe a behavioral correlation between irritability and performance and two executive functioning tasks. Other studies demonstrating irritability-related neural patterns also found no (Li et al., 2017) or mixed (Liuzzi et al., 2020; Tseng et al., 2019) results with respect to irritability-related differences in task performance. This suggests that

neuroimaging may be more sensitive to mechanisms of psychopathology dimensions and points to the value of neuroimaging data as complementary to behavior to generate a fuller picture of symptom-maintaining mechanisms.

There are several limitations in the present study. The sample size was modest (*N*=51) and covered a broad age range that necessitated correction for developmental differences, by adding age as a covariate across analyses. Given limited power and the cross-sectional design of the present study, age-related analyses that might have revealed developmental differences were not a focus of the present study. Additionally, our analyses were designed to test linear effects, yet it is possible that non-linear relationships between the variables of interest exist. In order to develop a more fine-grained understanding of the developmental factors that contribute to how irritability and executive functioning interact in the context of reward processing, replication in larger transdiagnostic samples examining these mechanisms among youths of more narrow age ranges is necessary. This study is also limited by its definition of executive functioning which was based on performance on two behavioral tasks. Future studies would benefit from better capturing the multifaced nature of executive functioning by examining both behavioral and functional definitions. Finally, this study is correlational in nature and its primary purpose is hypothesis generation with respect to the potentially ameliorating role of executive functioning on irritability-related neural aberrations during reward processing. It is unclear whether a causative relationship between irritability and executive functioning exists, and relatedly, whether increases in executive functioning performance would lead to irritability symptoms improvement. This will have to be tested longitudinally in clinical prevention and intervention trials. Nevertheless, the present findings point to mechanisms that may be used for intervention

development. For example, activities that promote executive functioning development in children could serve as a preventative measure throughout childhood.

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CHAPTER 5: CONCLUSION

Given the negative outcomes associated with pediatric irritability in childhood (Dougherty et al., 2015) and into adulthood (Savage et al., 2015; Stringaris et al., 2009), development of prevention and intervention options is critical and depends on characterization of irritability mechanisms. This study is the first to evaluate executive functioning as a potential moderator of the effect of irritability on reward processing and investigated the promising role of better executive functioning as a buffer for these reward processing deficits. Overall, our findings provide clues about executive functioning mechanisms involved in irritability that may present an opportunity for new prevention and intervention efforts. The present findings furthermore suggest that variability in executive functioning skills and how they relate to irritability may translate into individual differences in irritability maintenance and generation that may have important implications for the personalization of intervention approaches. This study is therefore is a crucial step toward understanding the interaction of top-down executive functioning processes in pediatric irritability, which provides the necessary groundwork to build mechanistic interventions for this common symptom with lifespan implications.

Sections of Chapter 5 have been accepted for publication in Psychiatry Research: Neuroimaging, 2022. The dissertation author was the primary researcher and author of this material with co-authors Palumbo, Danielle., Wakschlag, Lauren. S., Dougherty, Lea. R., and Wiggins, Jillian Lee.

TABLES

Table 1. Demographic and clinical characteristics

Characteristics	**Full Sample (N=51)**
Age, years, mean (SD)	13.80 (1.94)
Range	9.69-19.44
Pubertal Status, mean (SD)	2.45 (.66)
Sex, % female	52.94%
Hispanic Ethnicity, valid %	37.78%
Race, valid %	
African American	6.67%
Multiracial	20.00%
White	57.78%
Other	15.56%
Mother's Education, valid %	
High School	2.30%
Some College	23.30%
Standard College Degree	41.90%
Graduate Professional Training	32.60%
Cognitive Flexibility, mean (SD)	101.59 (15.67)
Range	70-137
Inhibitory Control, mean (SD)	90.96 (12.82)
Range	67-119
Irritability, parent-child average	2.16 (1.78)
Range	0-7.5
Externalizing Symptoms	6.83 (7.20)
Range	0-25
Depression, mean (SD)	9.14 (9.72)
Range	0-45
Anxiety, mean (SD)	15.08 (11.35)
Range	0-44

Note: SD=Standard Deviation; cognitive flexibility=age-corrected standard score on the NIH Toolbox Dimensional Change Card Sort task; Inhibitory control=age-corrected standard score on the NIH Toolbox Flanker task; irritability=score on Affective Reactivity Index; externalizing symptoms = raw score on externalizing subscale on Child Behavior Checklist; depression=score on parent-rated Mood and Feelings Questionnaire; anxiety=score on parent-rated Screen for Child Anxiety and Related Disorders; Statistically significant group differences are bolded. Missing data: pubertal status, n = 4; race, n= 1; ethnicity, n= 1; mother's education, n=8; depression, n=3; externalizing symptoms, n=11.

Table 2. Interactions of interest

Interactions examined	***Meaning of interaction with respect to neural patterns***
Reward Anticipation	
Executive Functioning x Irritability	Examines whether neural patterns during anticipation depend on irritability and executive functioning level regardless of reward condition (reward vs. no reward).
Executive Functioning x Irritability x Reward Condition	Examines whether neural patterns during anticipation depend irritability and executive functioning level, as well as on reward condition (reward vs. no reward).
Performance Feedback	
Executive Functioning x Irritability	Examines whether neural patterns during performance feedback depend on irritability and executive functioning level regardless of feedback condition (reward vs. no reward & hit vs. miss).
Executive Functioning x Irritability x Reward Condition	Examines whether neural patterns during performance feedback depend on irritability and executive functioning as well as reward condition (reward vs. no reward), but regardless of performance (hits vs. misses).
Executive Functioning x Irritability x Performance	Examines whether neural patterns during performance feedback depend on irritability and executive functioning as well as performance (hit vs. no miss), but regardless of reward condition (reward vs. no reward).
Executive Functioning x Irritability x Reward Condition x Performance	Neural patterns during performance feedback depend on irritability and executive functioning level as well as reward condition (reward vs. no reward) and performance (hits vs. misses).

Table 3. Significant clusters of interest resulting from whole-brain analyses

REWARD ANTICIPATION						
ACTIVATION						
Executive Functioning x Irritability x Reward Condition						
k	**F**	**x**	**y**	**z**	**BA**	**Region**
218	30.9	7	-97	8	18,17	Right Cuneus
CONNECTIVITY						
SEED: Left Ventral Striatum						
Executive Functioning x Irritability						
k	**F**	**x**	**y**	**z**	**BA**	**Region**
137	20.8	9	-95	0	18,17	Right Cuneus
88	17.6	-19	-99	4	18	Left Cuneus
SEED: Right Ventral Striatum						
Executive Functioning x Irritability						
k	**F**	**x**	**y**	**z**	**BA**	**Region**
204	19.8	25	-91	-18	18	Right Cuneus
PERFORMANCE FEEDBACK						
ACTIVATION						
Executive Functioning x Irritability						
k	**F**	**x**	**y**	**z**	**BA**	**Region**
196	32.6	-27	-1	-22	38	Left Uncus/Amygdala
105	26.9	31	1	10	-	Right Putamen
93	23.1	-7	7	36	32	Left Cingulate Gyrus
64	18.2	-15	-25	40	31	Left Cingulate Gyrus
Executive Functioning x Irritability x Reward Condition						
k	**F**	**x**	**y**	**z**	**BA**	**Region**
102	30.3	-49	21	4	45,47	Left Inferior Frontal Gyrus
87	16.4	-59	-37	-10	21	Left Middle Temporal Gyrus
72	25.4	-39	-23	-22	20	Left Fusiform Gyrus
Executive Functioning x Irritability x Performance Feedback						
k	**F**	**x**	**y**	**z**	**BA**	**Region**
83	19.5	-15	41	-2	10,32	Left Anterior Cingulate
73	23.9	7	-25	4	-	Right Thalamus
Executive Functioning x Irritability x Reward Condition x Performance Feedback						
k	**F**	**x**	**y**	**z**	**BA**	**Region**
89	24.6	-59	-17	42	6,4	Left Precentral Gyrus

Table 3 continued. Significant clusters of interest resulting from whole-brain analyses

CONNECTIVITY						
SEED: Right Ventral Striatum						
Executive Functioning x Irritability x Performance Feedback						
k	**F**	**x**	**y**	**z**	**BA**	**Region**
68	13.9	39	13	30	9	Right Middle Frontal Gyrus
SEED: Left Amygdala						
Executive Functioning x Irritability						
k	**F**	**x**	**y**	**z**	**BA**	**Region**
127	26.5	53	-29	-12	20,21	Right Middle Temporal Gyrus

BA=Brodmann area; Graphical representations of the interaction effects of cluster are presented in Figures 1-3; no significant clusters emerged in the analyses for any interactions that are not listed. Since the scan protocol was not optimized for cerebellar coverage, cerebellar clusters were not investigated in the present analyses but are listed in Supplemental Tables S3-4. Clusters that were outlier driven are also not listed here or further discussed but are listed in Supplemental Tables S3-4. For all contrasts df=1,48.

FIGURES

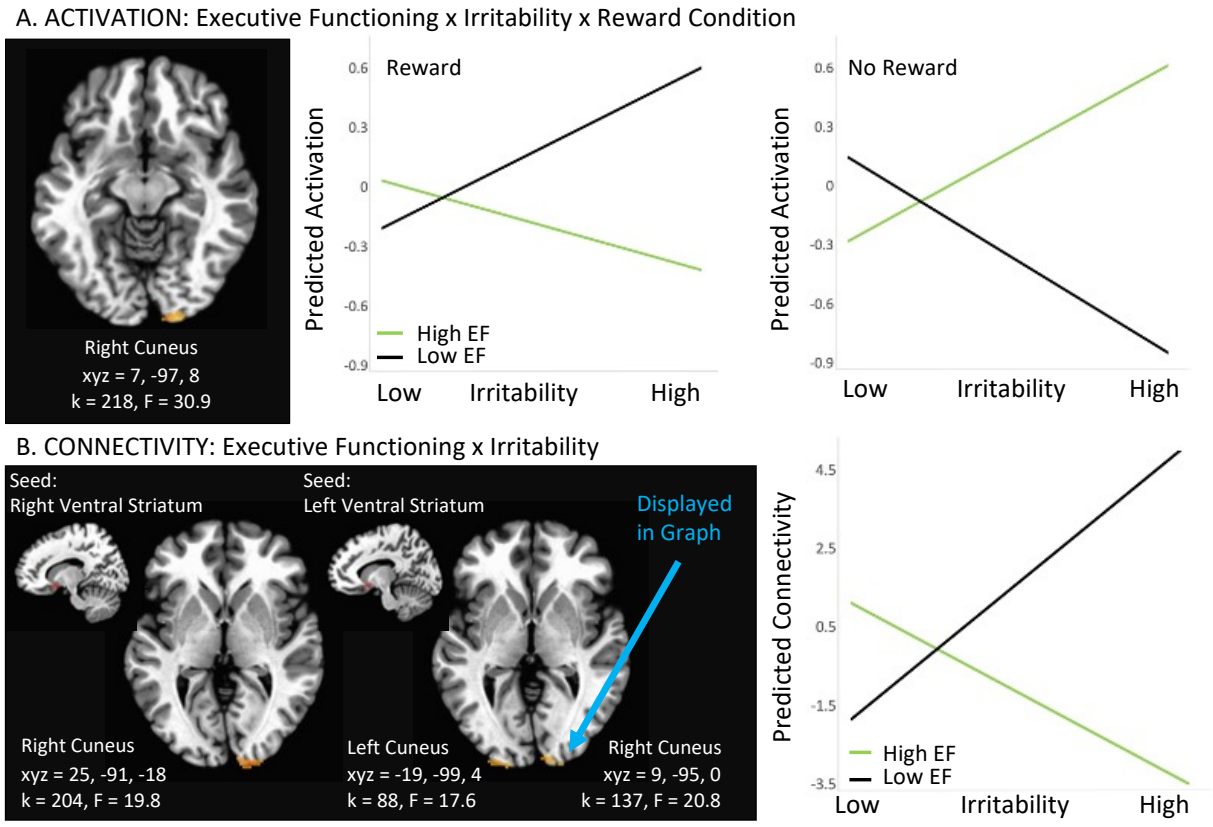

Figure 1. Moderating effect of executive functioning on irritability-related neural processes during reward anticipation. For illustrative purposes, graphs in all figures display predicted brain activation or connectivity values for indicated clusters based on the minimum and maximum of irritability scores (low=0, high=7.5) and executive functioning standard scores (high=114.5, low=75) in the present sample.

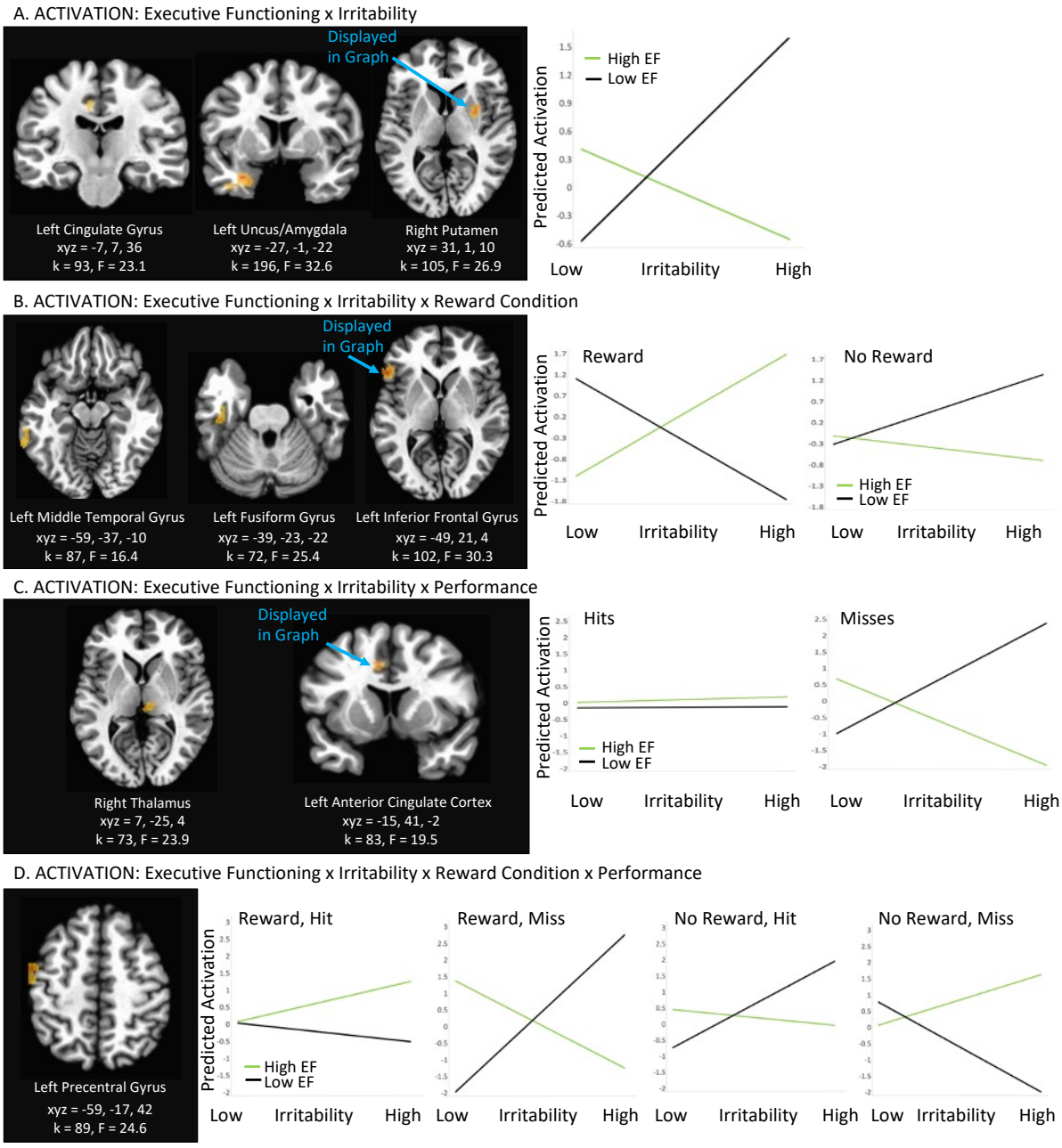

Figure 2. Moderating effect of executive functioning on irritability-related neural activation during performance feedback.

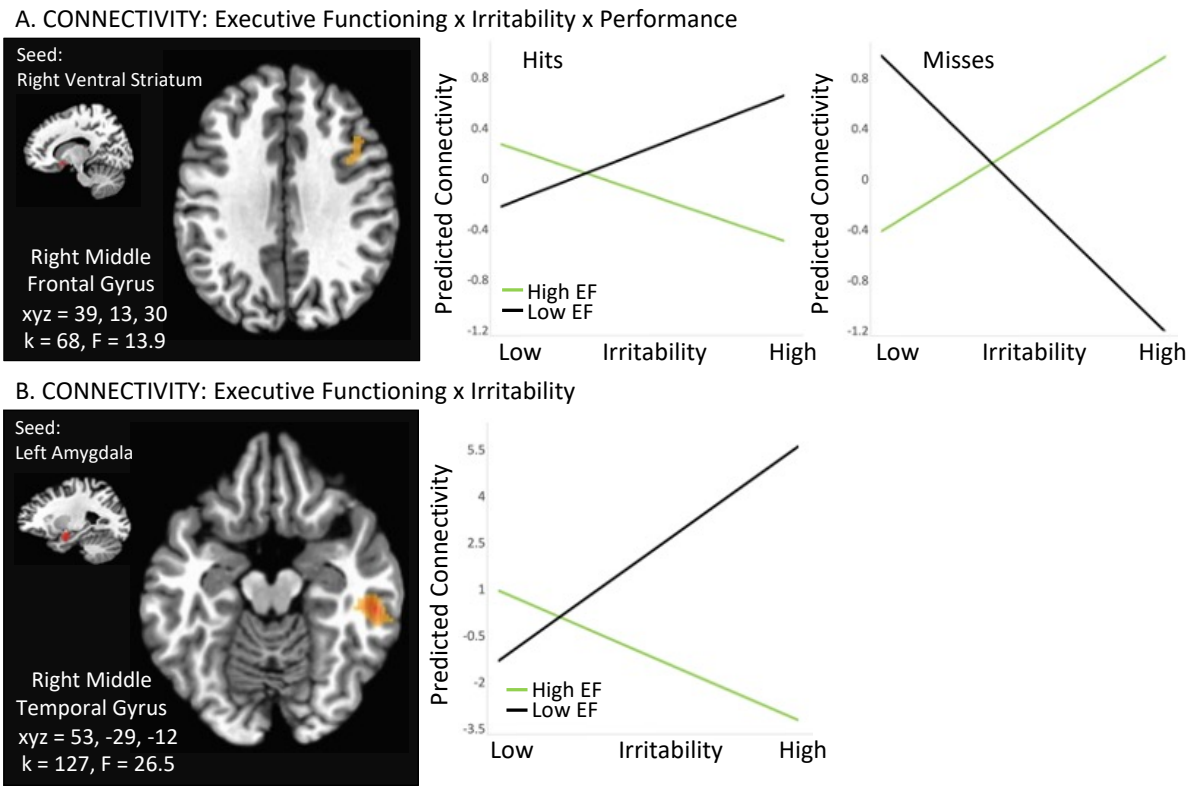

Figure 3. Moderating effect of executive functioning on irritability-related neural connectivity during performance feedback.

APPENDIX

Participants Sources and Recruitment

Three clinical trials served as recruitment sources for the present study: 1) an ongoing clinical trial (NCT03176004) of an eight-week attention bias modification training program (Subsample 1**,** n=33), 2) a clinical trial (NCT01147614) testing the efficacy of a brief behavioral intervention for depression and anxiety delivered in primary care (Subsample 2, n=14), 3) a clinical trial (NCT02021578) evaluating a Family Depression Prevention intervention program targeting parents with a history of depression and their at-risk children (Subsample 3, n=4). Data collection procedures were identical across recruitment sources using the same scanner between November 2016 and May 2018. Participants were provided with monetary compensation and a photo of their brain.

Subsample 1. Recruitment efforts for this clinical trial were facilitated through flyers posted in the community describing that the study aims to learn whether attention training can help youth with irritability and/or anxiety. A clinical diagnosis was not required for participation in this original clinical trial. Children and their mothers were invited to participate in the current fMRI study at the baseline appointment of the clinical trial. The original clinical trial referred 79 families to the present fMRI study and of those 35 children passed initial phone screening for fMRI contraindicators and volunteered to complete neuroimaging procedures. Two children were excluded from the present study. One was excluded because they withdrew consent from the current study and were not scanned due to claustrophobia and another one was excluded due to missing NIH toolbox data. The final sample consisted of 33 usable datasets. The present fMRI study included participants from all arms of the original clinical trial (treatment, sham control, no

treatment control) and data were collected within the first two weeks of active treatment and sham treatment (i.e., <25% of sessions).

Subsample 2. Participants who were originally enrolled in the brief behavioral intervention study for depression and anxiety met full or probable DSM-5 criteria for a primary anxiety and/or depressive disorder at the baseline assessment of the original clinical trial (see Weersing et al., 2017 for complete methodology). Recruitment to the present fMRI study occurred 2-7 years later by contacting parents of participants who were randomized to the brief behavioral intervention arm of the study at the local site who consented to further contact and were not lost to follow-up by the final intervention follow-up timepoint (n=44). Of those, 17 passed eligibility criteria and volunteered to participate in the current study which was completed in 1-2 sessions. The present analyses included data from 14 individuals. Participants were excluded because they declined completion of the fMRI scan (n=1) and due to data acquisition errors (n=2).

Subsample 3. Participants in the original Family Depression Prevention study were considered at risk for depression because at least one parent met criteria for a current or past DSM-5 depressive disorder. Families who were enrolled in the control arm of the Family Depression Prevention study and expressed interest in participating in the current fMRI study were referred. Eight families were contacted and 4 youths from 3 families participated and were included in the current analyses. One participant from Subsample 1 and two from Subsample 2 also participated in the Family Depression Prevention study (these individuals are not included in the subject count for the Subsample 3 recruitment source as this was not how they were recruited to the present fMRI study).

Additional Symptom Measures

The Screen for Child Anxiety and Related Disorders (SCARED; Birmaher, 1997), the Mood and Feelings Questionnaire (MFQ; Angold et al., 1987), Child Behavior Checklist (CBCL; Achenbach et al., 2001) captured anxiety, depression, and externalizing symptoms respectively. These measures were used to evaluate the potential confounding impact of concurrent anxiety, depression, and externalizing symptoms on the observed pattern of fMRI findings.

Additional Information on Measures of Executive Functioning

Cognitive flexibility. The NIH Toolbox Dimensional Change Card Sort task measured cognitive flexibility. During the task, youths are presented with two target pictures that vary along two dimensions (shape [e.g., rabbit/boat] and color [e.g., white/green]). The task consists of a cue period during which a word cue indicates whether cards should be matched according to shape or color, and a test-stimulus period during which the participant is shown a third shape that matches one of the other shapes. The participant is instructed to tap the correct shape according to the cue.

Inhibitory control. The NIH Toolbox Flanker task was administered to measure inhibitory control. The task goal is to indicate the left-right orientation of a centrally presented stimulus (an arrow pointing to the left or right) while inhibiting attention to four other arrows (two on each side of the target arrow) that may be pointing in the same (congruent) or the other direction (incongruent).

Score calculation. Standard scores were computed for each task via the NIH toolbox algorithm, based on accuracy and reaction time. Age-uncorrected standard scores were used, with age added as a covariate in analyses, for three reasons: 1) Adding age as a covariate in the

whole-brain regression models also allowed for correction of age-related differences in other variables of interest in the present analyses, given important changes in brain development (Brown et al., 2012; Fjell et al., 2012; Jernigan et al., 2016) and irritability (Copeland et al., 2015). 2) Akshoomoff et al. (2014) demonstrated that performance on the NIH toolbox executive functioning measures changes across development in a non-linear fashion, such that there are large performance improvements before age 10 with much smaller changes after age 10. All except two participants (ages 9.67 and 10.11) were above age 11, and the relation between mean uncorrected executive functioning scores and age in the present sample is linear and of small to medium size (r=.26). 3) Uncorrected and age-corrected standard scores are highly correlated (r=.87). Nevertheless, supplemental analyses were conducted to demonstrate stability of results when the youngest two participants were excluded. All clusters reported in this study remained significant without these participants, yet they were retained in the analyses to maximize power.

Demographic and Behavioral Data Analysis

To evaluate the relationship of executive functioning performance to irritability levels, controlling for age, partial correlations between irritability and executive functioning were conducted. Associations between participant characteristics and variables of interest in the present study (irritability, executive functioning) were evaluated using Pearson correlation coefficients for continuous variables (age, depression, anxiety, externalizing symptoms), t-tests for binary variables (gender, ethnicity), and ANOVAs for variables with more than two categories (race, maternal education).

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