



Examining cognitive control and reward interactions in adolescent externalizing symptoms

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ABSTRACT

During adolescence, rapid development and reorganization of the dopaminergic system supports increasingly sophisticated reward learning and the ability to exert behavioral control. Disruptions in the ability to exert control over previously rewarded behavior may underlie some forms of adolescent psychopathology. Specifically, symptoms of externalizing psychopathology may be associated with difficulties in flexibly adapting behavior in the context of reward. However, the direct interaction of cognitive control and reward learning in adolescent psychopathology symptoms has not yet been investigated. The present study used a Research Domain Criteria framework to investigate whether behavioral and neuronal indices of inhibition to previously rewarded stimuli underlie individual differences in externalizing symptoms in $N = 61$ typically developing adolescents. Using a task that integrates the Monetary Incentive Delay and Go-No-Go paradigms, we observed a positive association between externalizing symptoms and activation of the left middle frontal gyrus during response inhibition to cues with a history of reward. These associations were robust to controls for internalizing symptoms and neural recruitment during inhibition of cues with no reward history. Our findings suggest that inhibitory control over stimuli with a history of reward may be a useful marker for future inquiry into the development of externalizing psychopathology in adolescence.

1. Introduction

Regulating impulses is integral to adaptive decision-making. A behavior may be rewarding in certain contexts, such as watching TV on the weekend, but not in other contexts, such as watching TV the night before an exam. However, if a behavior has previously been rewarding, resisting the impulse to engage in that behavior may be difficult (Shoda et al., 1990). Thus, monitoring and updating reward contingencies can facilitate flexible behavior (Del Arco et al., 2017), which may then promote adaptive decision-making (Lee and Carlson, 2015; McCormick and Telzer, 2017).

Adolescents undergo dopaminergic reorganization that supports developing control over motivated behavior. During adolescence, dopamine system changes drive increased plasticity in circuits

connecting midbrain, subcortical, and cortical regions that integrate motivation and executive processes (Mastwal et al., 2014). These changes, which include increases in ventral striatum and prefrontal cortex connectivity (Hoops and Flores, 2017) and dopaminergic neuron innervation from the midbrain to the prefrontal cortex (Padmanabhan and Luna, 2014), support reward learning and behavioral control over reward (Romer et al., 2017; Mastwal et al., 2014). The striatum translates motivational signals into action (Robbins and Everitt, 1996), while prefrontal regions such as the inferior frontal gyrus (IFG) and ventromedial prefrontal cortex (VMPFC) guide reward-related action selection. While the IFG supports inhibitory control (Rubia et al., 2003; Aron et al., 2014), the VMPFC encodes and updates the value of actions and stimuli across time (Gläscher et al., 2009; Jocham et al., 2011). Thus, the adolescent brain develops connections between the striatum and

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prefrontal cortex that support the ability to integrate reward learning into flexible goal-directed behavior (de Wit et al., 2012; Christakou et al., 2011).

Psychopathology symptoms emerge in adolescence (Costello et al., 2011), raising the possibility that disruptions in regions supporting control over motivated behavior may be related to risk for psychopathology. Regulating behavior in rewarding contexts may be specifically related to externalizing behaviors (Bjork and Pardini, 2015), a dimension of psychopathology characterized by defiance of authority, impulse control difficulties, and increased sensation-seeking (Bogg and Finn, 2010), behaviors which generally increase during adolescence (Moffitt, 1993). Consistent with this idea, adolescents with externalizing psychopathology demonstrate perseverative responding to previously rewarded cues during reversal learning (Fonseca and Yule, 1995; Byrd et al., 2014). This response perseveration has been associated with perseverative striatal activation and reduced recruitment of cognitive control regions (Gatzke-Kopp et al., 2009), suggesting that disruption in corticostriatal function may impact the ability to flexibly adapt behavior to reward contingency shifts resulting in externalizing psychopathology.

Better understanding this link is critical, however, most studies examining externalizing psychopathology have studied cognitive control and reward separately. Previous work employing executive functioning tasks such as the Go-No-Go and Stop Signal Tasks have found impaired cognitive control and reduced prefrontal cortex recruitment in externalizing psychopathology (Castellanos-Ryan et al., 2014; Rubia et al., 2005; Wetherill et al., 2013). Research using reward conditioning paradigms such as the Monetary Incentive Delay Task have revealed associations between externalizing symptoms and altered striatal function during conditioning (Bjork et al., 2010; Gatzke-Kopp et al., 2009; Cohn et al., 2015). However, understanding the interaction of reward learning and cognitive control may elucidate the etiology of these symptoms as they are proposed to result from difficulty exerting motivational control (Rubia, 2011; Bjork and Pardini, 2015). It may also be that individual differences in executive function drive differences in reward-related behavior, given that domain-general behavioral disinhibition has been found to underly risk for externalizing disorders (Iacono et al., 2008; Tarter et al., 2003). However, current paradigms are unable to directly compare inhibitory control over responses which are previously unrewarded (motorically prepotent) vs previously rewarded (motorically prepotent and salient due to reward history) in the same task.

The Conditioned Appetitive Response Inhibition Task (CARIT; Winter and Sheridan, 2014) assesses the interaction of reward learning with inhibitory control, by measuring the extent to which reward-conditioned stimuli disrupt response inhibition. By examining inhibition to previously rewarded and unrewarded stimuli in the same task, the CARIT directly compares neural responses to inhibitory control over these stimuli. This task demonstrates sensitivity to adolescent-onset changes in reward-cognition interactions, as adolescents begin to show adult-like performance patterns whereby reward history intrudes on behavioral control (Davidow et al., 2018). These age-related behavioral changes are linked to increased IFG-VMPFC coupling, reinforcing these regions as integral to value-based action selection (Davidow et al., 2018). In contrast, during early childhood, history of reward facilitates inhibitory control in the CARIT (Winter and Sheridan, 2014). Reward learning may impact inhibitory control through attention, as reward conditioning has been found to direct attention to reward-predicting cues (Anderson et al., 2011; Bourgeois et al., 2015). Changes in attentional processes would account for both reward-driven facilitation and disruption of inhibitory control differentially across age. Value-driven attentional capture has been associated with activation in the visual cortex, parietal cortex, and posterior cingulate (Small et al., 2003; Anderson et al., 2014; Peck et al., 2009). While previous work using the CARIT has characterized the developmental trajectory of neural and behavioral task performance, individual differences in regulating previously rewarded behavior remain unexplored.

The Research Domain Criteria framework conceptualizes psychopathology as a spectrum, whereby developmental processes range from normal to abnormal (Insel et al., 2010). Research suggests variation in externalizing symptoms in typically developing adolescents (Moffitt, 1993), which are likely on a continuum with externalizing psychopathology (Walton et al., 2011). Consistent with this framework, we used a sample of typically developing adolescents to test whether a link exists between inhibitory control over stimuli with a history of reward and externalizing symptoms.

We examined associations between self-reported externalizing symptoms and neural recruitment and behavior on the CARIT task. We predicted that externalizing symptoms would be associated with reduced inhibitory control over stimuli with a history of reward and reduced recruitment of the IFG and VMPFC when inhibiting responses to previously rewarded cues. Because not just externalizing psychopathology but also the onset of many psychiatric illnesses increases during adolescence (Costello et al., 2011), we included controls for internalizing psychopathology and examined associations with total psychopathology in separate analyses.

2. Methods

2.1. Participants and general study procedures

We utilized data from 61 adolescents aged 12–17 ($M_{age} = 14.8$, $SD_{age} = 1.8$; 48 % female), whose demographics are reported in Table 1. These adolescents were selected from a larger study of children, adolescents, and adults (Davidow et al., 2018) and were selected for the current analysis because they completed the Youth Self-Report Questionnaire (YSR; Achenbach and Rescorla, 2001) assessing symptoms of psychopathology. Participants were recruited from the Greater Boston area using online ads such as craigslist, ads on public transportation, and flyers posted in Boston and Cambridge. Exclusion criteria for the larger study included self- or parent-reported history of neurological disorders, head trauma, formal diagnosis of any psychological or learning disorder, having a native language other than English, and having an MRI contraindication. Participants provided informed assent and a parent or legal guardian provided permission to participate and informed consent. All procedures were approved by the Partners Human Research Committee Institutional Review Board at Massachusetts General Hospital/Harvard Medical School.

We excluded participants who lost at least two (out of three total) runs for concerns related to task performance and/or imaging data

Table 1
Sample characteristics ($n = 61$).

Characteristic	Mean (SD) or Count (%)	Min (Max)
Age in years	14.8 (1.8)	12 (17.9)
Female	29 (48.5 %)	
Race		
White/Caucasian	35 (57.3 %)	
Black/African-American	13 (21.3 %)	
Asian	4 (6.5 %)	
Native American/Alaska Native	1 (1.6 %)	
Bi-racial	4 (6.6 %)	
Unreported	4 (6.6 %)	
Ethnicity		
Latinx	12 (19.7 %)	
Youth Self-Report		
Externalizing		
T-score	46.3 (10.0)	29 (69)
Symptom count	7.5 (6.1)	0 (25)
Internalizing		
T-score	47.7 (9.9)	27 (68)
Symptom count	8.2 (6.4)	0 (29)
Total		
T-score	46.9 (10.7)	26 (66)
Symptom count	29.6 (19.1)	1 (70)

quality concerns. Participants were excluded for task performance if they performed with less than 50 % accuracy on Go trials and/or less than 25 % accuracy on No-Go-trials. For imaging data quality criteria see 2.5.3 *Motion and Nuisance Effects*. Five participants were excluded from the imaging analysis; two participants were excluded due to behavioral performance, two participants were excluded due to both behavioral performance and motion, and one participant was excluded due to ending the scan session early. The final imaging sample was 56 adolescents ($M_{age} = 14.8$; $SD_{age} = 1.8$; 45 % female). Those excluded did not differ on psychopathology symptoms or demographic variables.

2.2. Psychopathology symptoms

The Youth Self-Report Questionnaire (YSR; Achenbach and Rescorla, 2001) is a widely used child and adolescent self-report measure assessing behavioral and emotional problems along two broadband scales: Internalizing and Externalizing Problems. The YSR was used to obtain an externalizing, internalizing, and total symptom score for each participant. Externalizing Problems ($\alpha = 0.86$) were youth reported symptoms on the Rule-Breaking Behavior and Aggressive Behavior subscales. Internalizing Problems ($\alpha = 0.62$) were youth reported symptoms on the Anxious/Depressed, Withdrawn/Depressed, and Somatic Complaints

subscales. Total Problems ($\alpha = 0.60$) were youth reported symptoms on Externalizing Problems, Internalizing Problems, Social Problems, Thought Problems, Attention Problems and Other Problems. The validity and reliability for this measure has been well-documented and extensive normative data are available for children ranging from 11–18 years old (Achenbach and Rescorla, 2001).

2.3. Behavioral Task: Inhibitory control over stimuli with a history of reward

The Conditioned Appetitive Response Inhibition Task (CARIT; Winter and Sheridan, 2014; Davidow et al., 2018) was used to assess inhibitory control over stimuli with a history of reward. The task consisted of two phases: (1) a reward conditioning phase and (2) an inhibitory control phase. The first phase of the CARIT utilized a modified version of the Monetary Incentive Delay task (MID; Knutson et al., 2000; Fig. 1.A.). The second phase of the CARIT used conditioned cues from the MID as No-Go cues in a Go-No-Go paradigm (Fig. 1.B). While the MID was performed outside of the scanner, the inhibitory control phase was performed inside of the scanner. Both phases of the CARIT were practiced outside of the scanner.

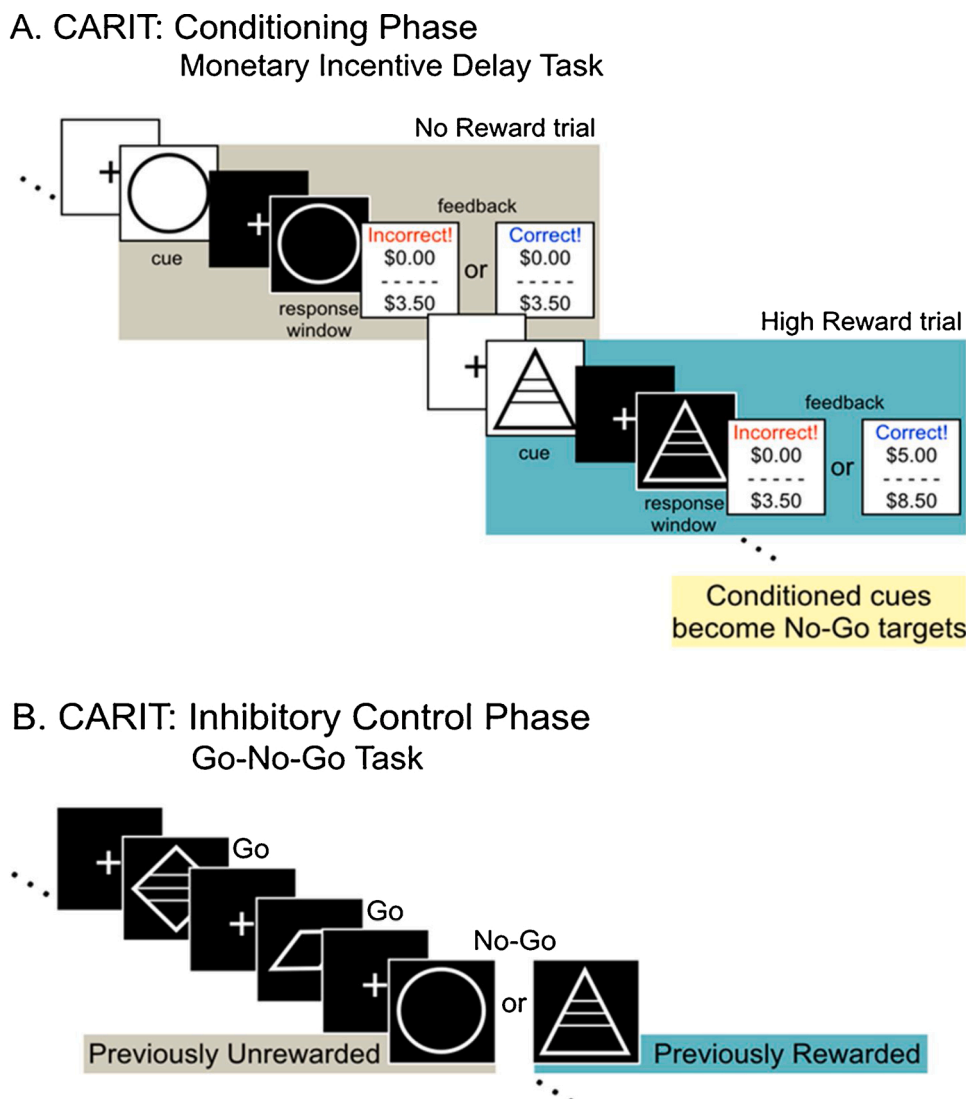


Fig. 1. The Conditioned Appetitive Response Inhibition Task (CARIT) assessing inhibitory control over previously rewarded targets. A. The reward conditioning phase (modified MID paradigm) B The inhibitory control phase. Figures reproduced with permission from Davidow et al (2018).

2.3.1. Phase I: reward conditioning (MID)

During each trial of the reward conditioning phase (Fig. 1.A.), the participant saw a black drawing of a shape against a white background (500 ms) indicating the type of trial. Then, a white fixation cross appeared against a black background as a signal to the participant to prepare for a rapid button press (jittered time interval; 2000–2375 ms, $M = 2187.5$, $SD = 140.2$). Next, a white line drawing of the previously cued shape appeared against a black background. While this cue was present on screen, the participant was instructed to press a button as quickly as possible to obtain the outcome. Then, the participant received feedback about whether the response was fast enough along with the resulting monetary outcome (1500 ms; Fig. 1.A.). The window of time that the cue remained on the screen, during which the participant needed to press a button to obtain the outcome, was adjusted dynamically during the task using a staircase algorithm to ensure an equal number of positive outcomes across participants (see Davidow et al., 2018 for details). Each participant's accuracy was set to 66 %.

The task consisted of 156 conditioning trials distributed over three blocks with 39 of each of the four shapes indicating four types of trials (e.g. Loss, No Reward, Low Reward, High Reward) presented in an intermixed pseudo-random order. Two shapes, a circle and a triangle, were used as conditioned cues; the rewarded shape was counterbalanced across participants. The unrewarded shape, for example the circle, was never associated with a monetary outcome (No Reward). The rewarded shape, for example the triangle indicated by three lines within the shape, was associated with a high monetary gain (High Reward); given that the participant correctly pressed during the response window, the participant had a 70 % chance of winning \$0.50 and a 30 % chance of winning \$5.00. Another two shapes were conditioned with a relatively small monetary gain (Low Reward; 70 % chance of winning \$0.10 and a 30 % chance of winning \$0.20) and a monetary loss (Loss; 70 % chance of losing \$1.00 and a 30 % chance of losing \$5.00) but were not carried forward to the inhibitory control phase of the task and are not analyzed here.

Following the final block of the task, the participants were asked to rate each cue based on how they felt about the cue (*valence rating*), how intensely they felt this way (*intensity rating*), and how important they felt that the cue was (*importance rating*). The participants rated these cues on a 5-point Likert scale from 1-very negative to 5-very positive (*valence rating*), 1-not at all intense to 5-very intense (*intensity rating*), and 1-not at all important to 5-very important (*importance rating*).

2.3.2. Phase II: inhibitory control (Go-No-Go)

This phase measured inhibitory control over stimuli with a history of reward by measuring the extent to which participants successfully withheld motor responses to previously rewarded cues in a Go-No-Go paradigm. This phase used two types of No-Go cues: the unrewarded cue (Previously Unrewarded target; PU) and the high reward cue (Previously Rewarded target; PR) from the MID. Critically, these targets no longer signaled reward. Therefore, false alarms to PR targets represented the residual impact of reward conditioning on performance.

Participants were instructed to press a button as quickly as possible to Go stimuli, which appeared frequently (264 trials total), and withhold button presses to No-Go stimuli, a group of either PR or PU targets that appeared occasionally (96 trials total). Go stimuli were line drawings of novel shapes that had not previously appeared in the conditioning phase. The order of presentation for all targets was pseudo-randomized.

Target stimuli were presented in a rapid event related design where Go and No-Go targets were presented for 600 ms followed by a jittered inter-stimulus-interval ranging from 500–4500 ms ($M = 1875$ ms, $SD = 1221$). Correct and incorrect responses were recorded during a 1100 ms response window beginning at the onset of the target. This phase consisted of three runs, each containing 120 trials.

2.4. Behavioral analysis

For the MID, motor response bias was calculated by subtracting average reaction time (RT) for high reward cues from the average RT for unrewarded cues (unrewarded > high reward RT). Higher values indicated more speeding to reward (i.e., greater response bias). In addition, self-report ratings for unrewarded cues were subtracted from self-reported ratings for high reward cues, generating three values representing the difference between high reward cues and unrewarded cues in valence, intensity, and importance (high reward > unrewarded self-report ratings). Greater values indicated greater subjective valuation of reward.

For the inhibitory control phase of the CARIT, accuracy scores on PU No-Go stimuli were subtracted from accuracy scores on PR No-Go stimuli (PR > PU accuracy). Lower values indicated poorer inhibitory control over stimuli with a history of reward.

To assess for the relationship between these behavioral measures and psychopathology symptoms, we used a multiple linear regression model in R (R Development Core Team, 2008), controlling for age and sex. We examined associations with externalizing symptoms with and without controlling for internalizing symptoms. Next, we examined associations with domain-general total psychopathology symptoms.

We regressed behavioral measures in the MID on symptoms to indicate how psychopathology symptoms may relate to differences in reward sensitivity through motor response bias and self-reported reward valuation. We regressed inhibitory control over stimuli with a history of reward on symptoms to indicate how psychopathology symptoms may relate to differences in the ability to inhibit previously rewarded behavior.

2.5. fMRI

2.5.1. MRI acquisition

Imaging data was acquired at the MGH/HST Athinoula A. Martinos Center for Biomedical Imaging on a 3 T CONNECTOM scanner using a 64-channel phased array head coil. A high-resolution T1-weighted multi-echo magnetization-prepared rapid gradient-echo (MEMPRAGE) image was acquired. This acquisition was accelerated with generalized auto-calibrating partially parallel acquisitions for registration parameters (TR = 2530 ms; TE = 1.61 ms, FA = 7°; array = 256 × 256, 208 slices, voxel resolution = 1.0 mm³, FOV = 256 mm).

Functional BOLD images for the inhibitory control phase of the CARIT were acquired in three runs of 124 volumes each (372 total volumes) of interleaved descending T2*-weighted echo-planar (EPI) volumes at oblique transverse orientation (TR = 2500 ms; TE = 30 ms; FA = 90°; array = 72 × 72; 39 slices; effective voxel resolution = 3.0 mm³, FOV = 216 mm). Participants viewed the CARIT task projected onto a screen in a mirror mounted on the head coil and used a button box compatible with the MR environment to make behavioral responses.

2.5.2. Preprocessing

Functional and anatomical brain image data processing and statistical analysis were performed in FMRIB's Software Library (FSL, www.fmrib.ox.ac.uk/fsl). Preprocessing included skull-stripping using the Brain Extraction Tool (BET; Smith, 2002), segmentation using FMRIB's Automated Segmentation Tool (FAST; Zhang et al., 2001), realignment and motion correction using estimates computed in MCFLIRT (Jenkinson et al., 2002), slice-time correction, and spatial smoothing using a Gaussian kernel of full width half maximum (FWHM) 5 mm, as described in Davidow et al. (2018).

2.5.3. Motion and nuisance effects

Nuisance regressors consisted of 24 regressors, comprised of 3-translational and 3-rotational estimates generated during preprocessing, their derivative, their square, and the square of the derivative. These estimates were submitted to Art software (<http://gablab.mit.edu/index.php>

/software) implemented through Nipype (Gorgolewski et al., 2011) to identify timepoints where there was greater than 0.9 mm relative translational motion for censoring (Siegel et al., 2014) and spikes in signal intensity greater than 3 standard deviations away from the participant mean for the run. Outlier timepoints were appended to the motion nuisance regressor file included in the GLM to be censored. Runs were excluded for imaging data quality concerns if there was a single relative movement greater than 5 mm and/or 15 % timepoints censored from motion and artifact detection.

2.5.4. fMRI group level statistical analysis

A general linear model (GLM) was constructed to estimate effects of task and control for events of non-interest. The GLM design for task events was comprised of equally weighted event onsets and durations for the six possible task events: correct and incorrect responses to PR No-Go targets, PU No-Go targets, and Go targets (Davidow et al., 2018; Meyer et al., 2020). All task regressors were convolved with the canonical hemodynamic response function using FSL FEAT. To test for the influence of reward history manipulation on successful inhibitory control in the brain, correct trials of Previously Rewarded (correct PR) No-Go cues were contrasted with correct trials of Previously Unrewarded (correct PU) No-Go cues while regressing out the effect of non-interest cues. Following typical FSL procedures, statistical analysis of functional images was conducted for each participant and each run. Then, the runs were combined in a fixed-effect analysis for each participant using the linear registration of functional images to MNI-template space.

Group level mixed-effect statistical analyses were performed in FSL FEAT with FLAME1. All group-level analyses were corrected for age and sex. The maps indicating successful inhibitory control over stimuli with a history of reward (correct PR > correct PU) were regressed on symptom scores to test for the effect of externalizing symptoms and domain-general psychopathology symptoms on neural recruitment during reward inhibition. All group-level results were thresholded in FSL using a voxel-wise Z-statistic of $Z = 2.3$ and a cluster threshold of $p = 0.05$ for a family-wise error correction of $FWE p < 0.05$.

For display purposes, activation parameter estimates for each participant were extracted from a 6 mm^3 sphere drawn around the peak of activation using FSL featquery, and activation values were converted into percent signal change.

3. Results

3.1. Sample characteristics

Demographics and scores from the Youth Self-Report are reported in Table 1. Externalizing and internalizing symptoms showed a positive correlation ($r = 0.52$, $df = 59$, $p < 0.001$), but were unrelated to age, sex, or ethnicity (all $|r|$'s < .21; all p 's > 0.10).

3.2. Behavioral performance

Here, we report results from the CARIT, beginning with the conditioning phase (Phase I) and then the inhibitory control phase (Phase II).

3.2.1. Phase I: reward conditioning (MID)

3.2.1.1. Main effects of task. There was a significant effect of reward conditioning on reaction time, such that participants responded more quickly to the high reward cues ($M = 225.6 \text{ ms}$) relative to the unrewarded cues ($M = 239.3 \text{ ms}$; $t(60) = 7.1$, $p < 0.001$). There was also a significant effect of reward conditioning on self-reported valuation, such that participants rated the high reward cues as more intense ($M_{\text{high}} = 4.38$, $M_{\text{unrewarded}} = 1.80$; $t(60) = 14.7$, $p < 0.001$), more important ($M_{\text{high}} = 4.52$, $M_{\text{unrewarded}} = 1.89$; $t(60) = 15.6$, $p < 0.001$), and more positive ($M_{\text{high}} = 4.64$, $M_{\text{unrewarded}} = 3.13$; $t(60) = 12.5$, $p < 0.001$) than

the unrewarded cues.

3.2.1.2. Association with externalizing psychopathology symptoms. We found that externalizing symptoms were not associated with motor response bias to high reward cues relative to unrewarded cues ($B = -0.49$, $df = 57$, $p = 0.13$). Similarly, externalizing symptoms were not associated with self-reported valuation of cues (all p 's > 0.29). These associations remained non-significant when controlling for internalizing symptoms (p 's > 0.30).

3.2.1.3. Association with total psychopathology symptoms. There was a non-significant effect of total psychopathology symptoms on motor response bias to reward ($B = -0.19$, $df = 57$, $p = 0.06$). There was a significant negative association between total symptoms and subjective intensity of reward ($B = -0.02$, $df = 57$, $p = 0.04$), such that differentiation between the high reward and unrewarded cues on self-reported affective intensity decreased as total symptoms increased. Total symptoms were not related to self-reported importance or valence of reward (all p 's > 0.25).

3.2.2. Phase II: inhibitory control (Go-No-Go)

3.2.2.1. Main effects of task. We defined response inhibition as accuracy on PU trials controlling for Go trial accuracy to account for individual differences in task-related behavior. Participants had significantly lower accuracy on PU No-Go targets ($M = 0.59$) than on Go targets ($M = 0.96$; $t(57) = 15.9$, $p < 0.001$), typical of Go-No-Go task performance.

The effect of previous reward conditioning on inhibition was termed inhibitory control over stimuli with a history of reward. Inhibitory control over stimuli with a history of reward was defined as accuracy on PR trials controlling for accuracy on PU trials to account for individual differences in inhibitory control. The difference in accuracy on PR No-Go targets ($M = 0.56$) relative to PU No-Go targets ($M = 0.59$) was not significant ($t(57) = 1.7$, $p = 0.09$).

3.2.2.2. Association with externalizing psychopathology symptoms. There was no association between externalizing symptoms and inhibitory control over stimuli with a history of reward ($B = -0.003$, $df = 54$, $p = 0.23$) or response inhibition ($B < -0.001$, $df = 54$, $p = 0.98$). In addition, externalizing symptoms were not related to changes in false alarms to PR relative to PU cues across runs ($B = -0.002$, $df = 48$, $p = 0.63$). These associations remained non-significant when controlling for internalizing symptoms (p 's > 0.80).

3.2.2.3. Association with total psychopathology symptoms. There was a non-significant effect of total symptoms on false alarms to PR relative to PU targets ($B < 0.001$, $df = 54$, $p = 0.08$). Total symptoms were unrelated to changes in false alarms to PR relative to PU cues across runs ($B < 0.001$, $df = 48$, $p = 0.69$) and response inhibition ($B < 0.001$, $df = 53$, $p = 0.89$).

3.3. fMRI results

3.3.1. Main effects of task

For the main effects of the inhibitory control phase we report on neural activation for our primary contrasts of interest: (1) successful inhibitory control over stimuli with a history of reward (correct PR > correct PU) (2) successful response inhibition (correct PU > correct Go). Successful inhibition over stimuli with a history of reward revealed a large cluster with peak activation in the cuneus that extended inferiorly into the fusiform and lingual gyrus, and two clusters in the bilateral occipital pole (Table 2; Fig. 2), potentially reflecting subtle visual differences between the cues (e.g. stripes in the PR cue). Successful response inhibition was associated with four large clusters spanning the

Table 2

Regions of peak activation associated with main effects of the inhibitory control phase of the CARIT ($n = 56$). Results thresholded using a voxel-wise threshold of $Z = 2.3$ and a cluster threshold of $p = 0.05$ for a family-wise correction of $p < 0.05$.

Contrast	Region of Peak Activation	Cluster Size	x	y	z	Z Value	
Successful Inhibition Over Stimuli with a History of Reward correct PR > correct PU	Cuneus	5297	2	-76	34	4.55	Cluster peak
	Occipital pole (R)	661	32	-92	0	5.46	Cluster peak
	Occipital pole (L)	586	-28	-92	-6	4.65	Cluster peak
Successful Response Inhibition correct PU > correct Go	Orbital frontal cortex (R)	10,878	30	20	-12	6.48	Cluster peak
	~Inferior frontal gyrus (R)						
	Middle temporal gyrus (R)	3970	52	-26	-6	5.56	Cluster peak
	Temporoparietal junction (R)		62	-40	28	5.45	Local max
	Middle frontal gyrus (L)	1928	-32	46	20	5.98	Cluster peak
	Insula (L)	1791	-30	18	-8	6.19	Cluster peak
	~Inferior frontal gyrus (L)						

Note: ~ = contiguous with, PR = Previously Rewarded, PU = Previously Unrewarded.

Successful inhibitory control over stimuli with a history of reward correct PR > correct PU

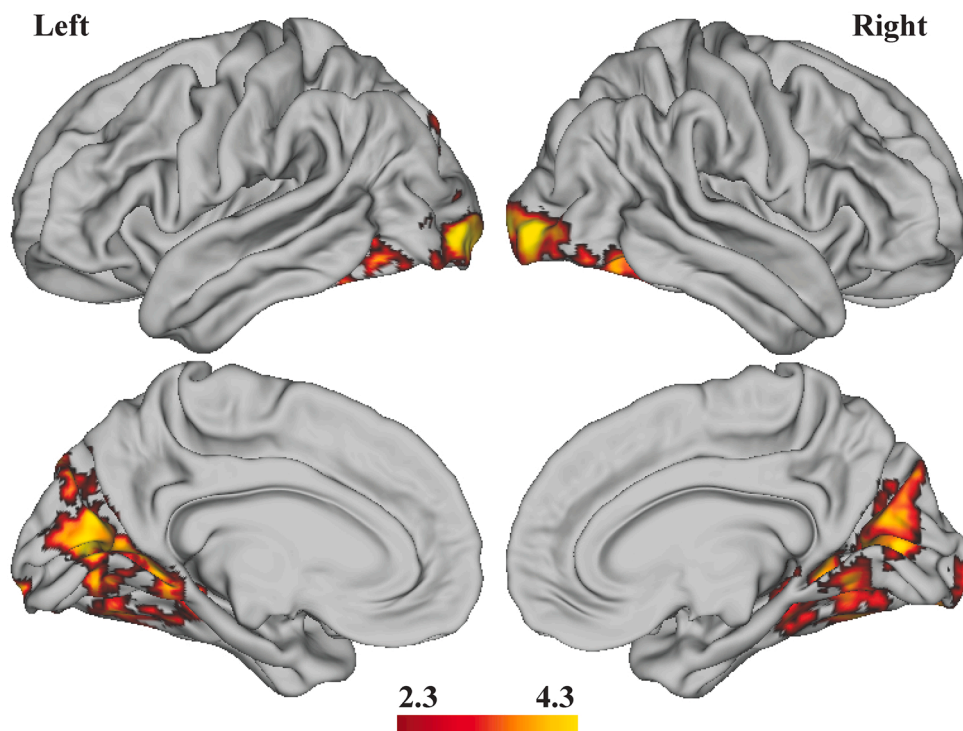


Fig. 2. Main effect of inhibitory control over Previously Rewarded targets ($n = 56$). These maps demonstrate increased recruitment of the cuneus, lingual gyrus, fusiform gyrus, and occipital cortex during successful inhibition to Previously Rewarded (PR) No-Go relative to successful inhibition to Previously Unrewarded (PU) No-Go targets (voxel-wise corrected $Z = 2.3$, cluster corrected $p < 0.05$).

dorsolateral prefrontal cortex, ventrolateral prefrontal cortex, temporal gyrus, and anterior cingulate cortex. Peak activation in these clusters was located in the right orbital frontal cortex, the right middle temporal gyrus, the left middle frontal gyrus, and the left insula. (Table 2; Fig. 3).

3.3.2. Association with externalizing psychopathology symptoms

During successful inhibition over stimuli with a history of reward, externalizing symptoms were associated with increased activation in the posterior cingulate, precuneus, parietal regions and left middle frontal gyrus (LMFG; Fig. 4.A.; Table 3). As externalizing symptoms increased,

activation for correct PR relative to correct PU trials increased in these areas. Activation in the inferior parietal and prefrontal regions were robust for controls for internalizing symptoms (Fig. 4.B.; Table 3). For display purposes, parameter estimates from the LMFG, using peak activation in this region associated with externalizing symptoms, were extracted and plotted with externalizing symptoms, excluding one subject whose studentized residuals were identified as an outlier at Bonferroni $p < 0.05$ (Fig. 4.C.). During successful response inhibition, externalizing symptoms were associated with decreased activation in the left precuneus and left superior parietal (Fig. 5.A.), which were

Successful response inhibition correct PU > correct Go

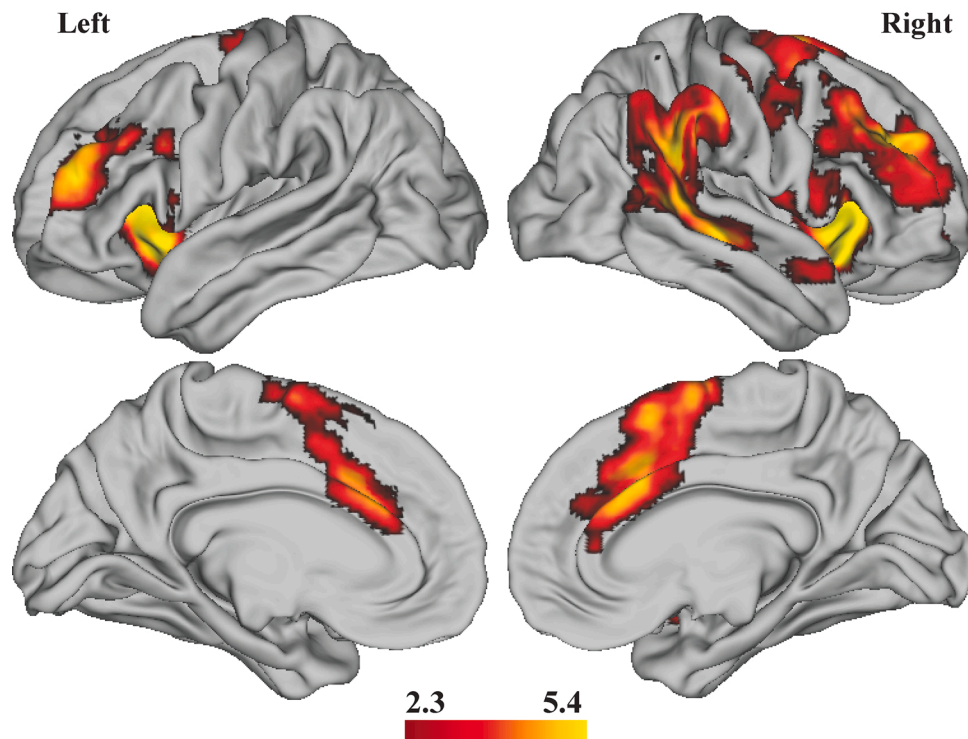


Fig. 3. Main effect of successful response inhibition to Previously Rewarded (PU) targets relative to successful responses to Go targets ($n = 56$). These maps demonstrate robust positive associations with regions typically recruited in response inhibition tasks, including the inferior frontal gyrus and the anterior cingulate cortex (voxel-wise corrected $Z = 2.3$, cluster corrected $p < 0.05$).

robust for controls for internalizing symptoms (Fig. 5.B.).

3.3.3. Association with total psychopathology symptoms

During successful inhibition over stimuli with a history of reward, total symptoms were associated with four clusters in the frontal cortex, parietal cortex, precuneus, and posterior cingulate. Peak activation in these clusters was located in the precuneus, left intracalcarine cortex, left superior frontal cortex, and the left lateral occipital cortex (Fig. 6, Table 3). Total symptoms were not associated with changes in activation during successful response inhibition.

4. Discussion

The present study assessed whether, during adolescence, individual differences in the ability to regulate behavior to stimuli with a previous reward history were associated with individual differences in psychological functioning, particularly in the externalizing domain. Adolescence is a period of dramatic change in reward learning and regulatory abilities, whereby individuals are increasingly able to integrate information about past behaviors and outcomes to guide future-oriented decisions (Romer et al., 2017). Conversely, adolescent-onset externalizing disorders are characterized by difficulty in flexibly adapting behavior in response to shifts in action-outcome contingencies (Rubia, 2011; Byrd et al., 2014). Therefore, reductions in the ability to regulate previously rewarded behavior may be a mechanism by which individual differences in externalizing symptoms emerge. To date, few studies have measured the direct interaction of history of reward and inhibitory control. By measuring the extent to which history of reward disrupts inhibitory control, the CARIT task can disentangle reward learning from executive control processes.

Although we did not observe an association between externalizing symptoms and behavioral performance when inhibiting responses to previously rewarded stimuli, we observed associations with neural recruitment. Externalizing symptoms were associated with alterations in the fronto-parietal control and default mode networks, specifically with increased activation in the left middle frontal gyrus (MFG), parietal cortex, and posterior cingulate when successfully inhibiting responses to PR targets relative to PU targets. Furthermore, activation within the MFG was robust for controls for internalizing symptoms. To be successful at inhibiting responses to PR targets, participants with more externalizing symptoms recruited the left MFG to a greater degree. This increased activation, because it is observed in the context of no differences in task performance, may reflect a compensatory response. The MFG has been associated with executive control (Badgaiyan, 2000), working memory (McNab and Klingberg, 2008), and representation of task rules (Dixon et al., 2018). Previous work has demonstrated associations between externalizing psychopathology and reduced MFG function during inhibitory control tasks, including developmentally-stable hypo-activation in the left MFG associated with externalizing symptoms during inhibitory control (Heitzeg et al., 2014; Quach et al., 2020). Interestingly, we predicted that we would observe associations with recruitment of the IFG based on previous work indicating that the IFG subserves inhibitory control (Rubia et al., 2003; Aron et al., 2014). However, we found no associations between IFG recruitment in this task and externalizing symptoms. Adolescents with externalizing symptoms may recruit different frontal regions for successful performance on the CARIT, which integrates inhibitory control with reward learning, than on other inhibitory tasks which do not utilize stimuli with imbued value. Future research using tasks that assess the interaction of inhibitory control with reward in adolescents with

Successful inhibitory control over stimuli with a history of reward correct PR > correct PU

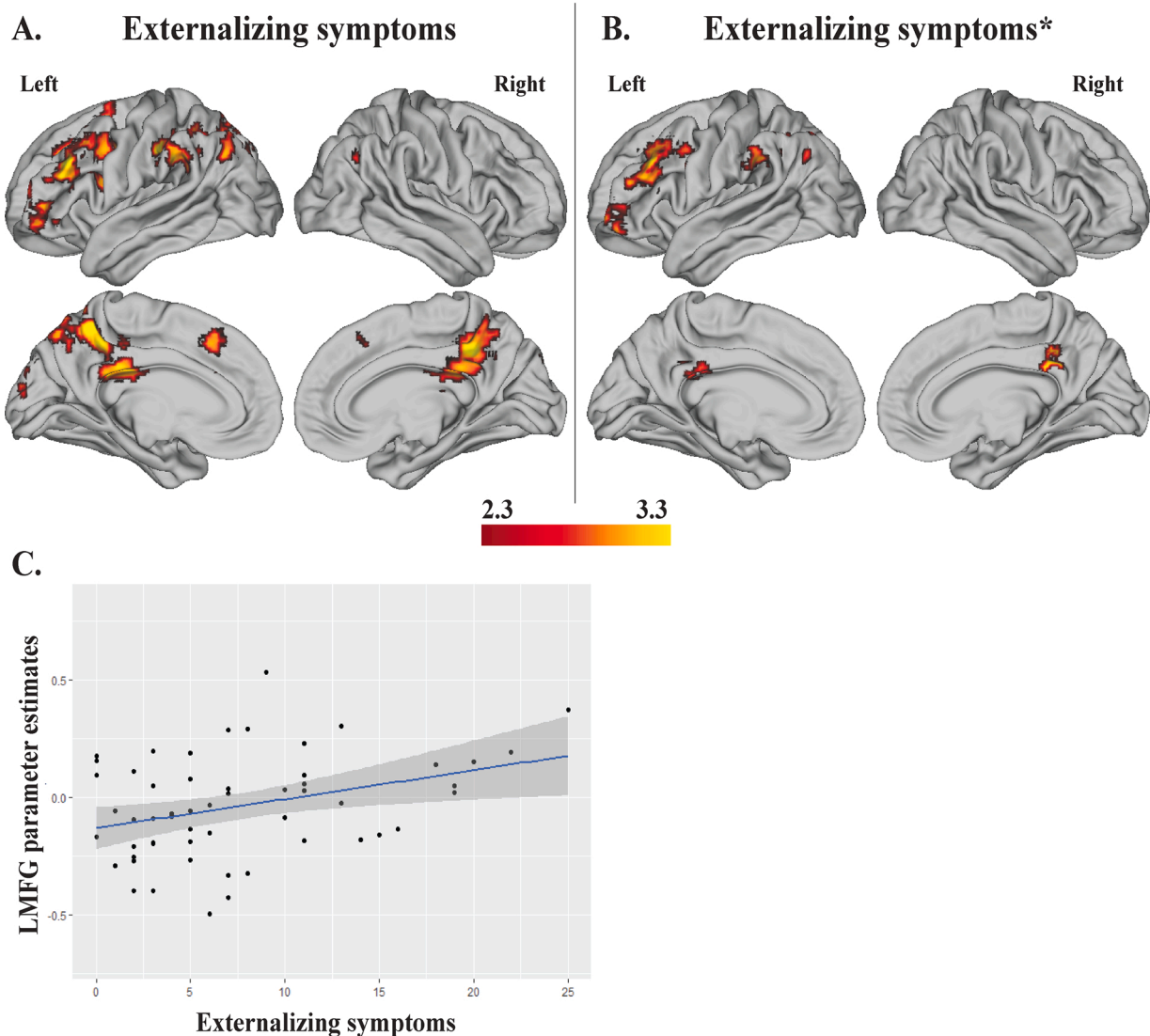


Fig. 4. Successful inhibitory control over previously rewarded (PR) relative to previously unrewarded (PU) targets, regressed on externalizing symptoms ($n = 56$). Voxel-wise corrected $Z = 2.3$ and cluster-corrected $p < 0.05$. * = controlled for internalizing symptoms. A. Controlled for age and sex. These maps demonstrate positive correlation in the left ventrolateral prefrontal cortex, left middle frontal gyrus, and left inferior parietal cortex. B. Controlled for age, sex, and internalizing symptoms. These maps demonstrate that increased activation in prefrontal regions associated with externalizing symptoms is robust for controls for internalizing symptoms. C. Scatterplot of externalizing symptoms against left middle frontal gyrus (LMFG) BOLD-signal extracted during successful inhibitory control over stimuli with a history of reward, for visualization purposes only (MNI152 coordinates: $x = -44$, $y = 30$, $z = 30$; seed radius = 6 mm^3).

externalizing psychopathology is needed to replicate these findings.

It has been suggested that risk for externalizing psychopathology may be best captured using broad dimensional constructs spanning affective, cognitive, and behavioral domains (Tarter et al., 2003; Iacono et al., 2008). Risk for externalizing psychopathology has been postulated to occur from both impaired top-down executive function and sensitivity in bottom-up reward processing regions (Iacono et al., 2008; Bjork and Pardini, 2015), and existing literature has demonstrated associations between externalizing symptoms and impaired frontal recruitment during cognitive control (Rubia et al., 2005; Castellanos-Ryan et al., 2014) and reward paradigms (Gatzke-Kopp et al., 2009; Castellanos-Ryan et al., 2011). Here, we extended previous research by demonstrating that this effect was most strong for response inhibition in the context of reward history. By comparing activation during successful inhibition to PR targets relative to PU targets, we held response

inhibition processes constant, thus isolating the effect of reward history on inhibitory control. Interestingly, while externalizing-related differences were specific to inhibition in a reward context, externalizing symptoms were unrelated to differences in bottom-up reward-processing regions. These findings suggest that disinhibition associated with externalizing psychopathology may be driven by domain-general impairments in executive function, which may nevertheless impact affective domains requiring cognitive control. We also examined associations between externalizing symptoms and response inhibition to PU cues. In this sample, we did not observe that externalizing symptoms were associated with differences in prefrontal recruitment on these trials. Given that we used a typical sample without psychopathology, these findings may indicate that measures assessing the impact of reward history on inhibitory control are more sensitive than typical inhibitory control tasks to individual differences in subclinical symptoms. Future

Table 3

Regions of peak activation when successfully inhibiting to Previously Rewarded (PR) relative to Previously Unrewarded (PU) targets associated with psychopathology symptoms, controlled for age and sex ($n = 56$). Results thresholded using a voxel-wise threshold of $Z = 2.3$ and a cluster threshold of $p = 0.05$ for a family wise correction of $p < 0.05$.

Contrast	Region of Peak Activation	Cluster Size	x	y	z	Z Value	
Successful Inhibition Over Stimuli with a History of Reward correct PR > correct PU <i>Externalizing symptoms</i>	Precuneus	6026	8	-42	40	4.20	Cluster peak
	Inferior parietal (L)		-42	-48	34	4.17	Local max
	Middle frontal gyrus (L)	2491	-44	30	30	4.11	Cluster peak
<i>Externalizing symptoms*</i>	Inferior parietal (L)	1792	-42	-48	34	4.63	Cluster peak
	Frontal pole (L)	1460	-44	54	4	3.88	Cluster peak
	~Middle frontal gyrus (L)						
<i>Total symptoms</i>	Precuneus	4857	8	-42	42	4.33	Cluster peak
	~Posterior cingulate, superior parietal (L)						
	Intracalcarine cortex (L)	768	-12	-66	4	3.94	Cluster peak
	Superior frontal gyrus (L)	570	-24	6	54	3.78	Cluster peak
	Middle frontal gyrus (L)		-28	12	46	3.43	Local max
Lateral occipital cortex (L)	527	-30	-88	38	3.77	Cluster peak	

Note: * = controlled for internalizing symptoms, ~ = contiguous with, PR = Previously Rewarded, PU = Previously Unrewarded.

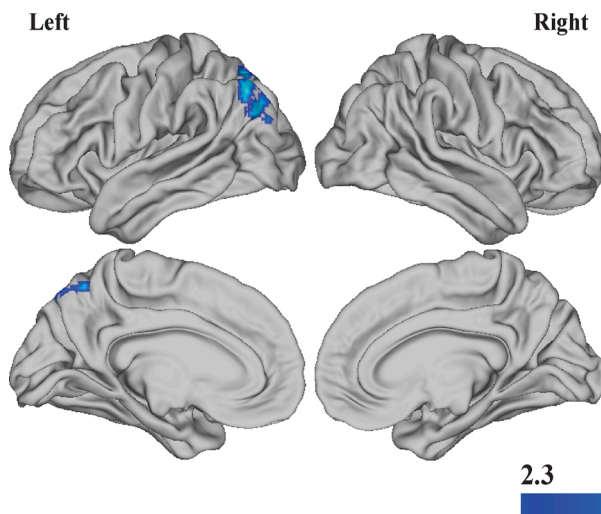
work should examine these associations in participants with externalizing psychopathology.

Cognitive risk-factors underlying externalizing psychopathology similarly predict risk for substance use disorders, including impaired performance on and reduced prefrontal recruitment during executive functioning tasks (Squeglia and Cservenka, 2017; Tervo-Clemmens

et al., 2017). Furthermore, externalizing psychopathology has been linked to increased risk for substance use initiation and substance use disorders (Tarter et al., 2003; Squeglia et al., 2017). Thus, our findings may have implications for the development of substance use disorders. In support of this possibility, reduced MFG function has been consistently identified in adolescents with and at risk for problematic

Successful response inhibition correct PU > correct Go

A. Externalizing symptoms



B. Externalizing symptoms*

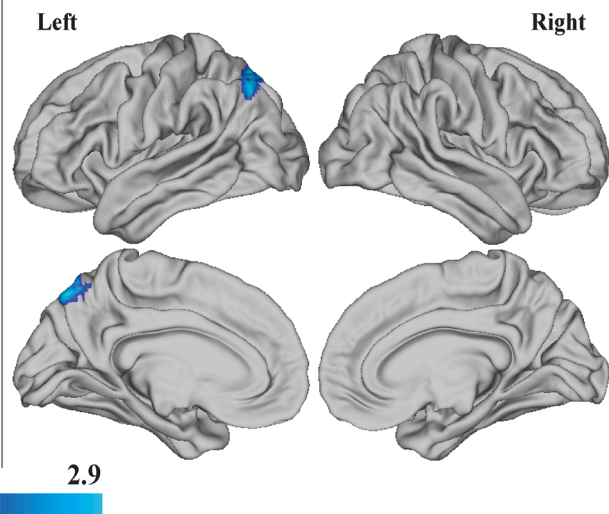


Fig. 5. Successful response inhibition to Previously Unrewarded (PU) targets regressed on externalizing symptoms ($n = 56$). * = controlled for internalizing symptoms. A. Controlled for age and sex. These maps demonstrate that externalizing symptoms are associated with decreased activation in parieto-occipital regions when successfully inhibiting responses to PU targets relative to successful responses to Go targets. Peak activation in left superior parietal ([MNI152 coordinates: $x = -42$, $y = -72$, $z = 44$]; z -value = 3.74, 574 voxels; voxel-wise corrected $Z = 2.3$ and cluster corrected $p < 0.05$). B. Additionally controlled for internalizing symptoms. These maps demonstrate that decreased activation in parieto-occipital regions associated with externalizing symptoms is robust for controls for internalizing symptoms.

Successful inhibitory control over stimuli with a history of reward correct PR > correct PU

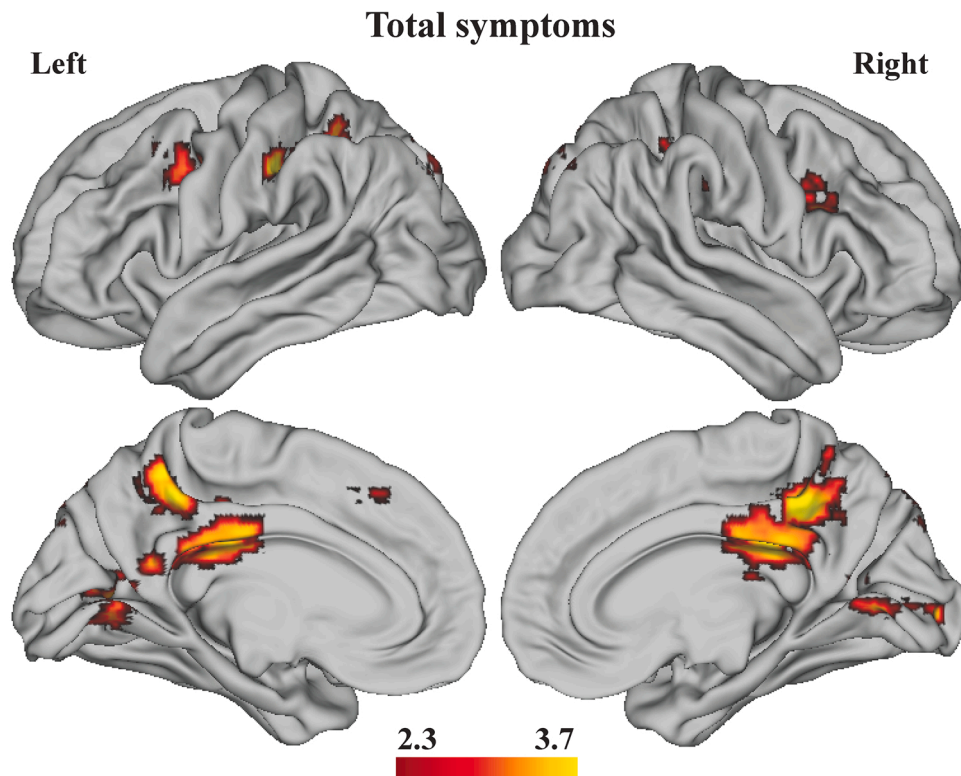


Fig. 6. Successful inhibitory control to previously rewarded (PR) relative to previously unrewarded (PU) targets ($n = 56$) regressed on total psychopathology symptoms, controlling for age and sex. Maps demonstrate a positive correlation in the precuneus and posterior cingulate, extending into the left superior frontal gyrus, left postcentral gyrus, and left superior parietal cortex (voxel-wise corrected $Z = 2.3$, cluster corrected $p < 0.05$).

substance use during inhibitory control tasks (Hardee et al., 2014; Heitzeg et al., 2015), suggesting shared risk-related effects in this region. Prospective research using the CARIT task is needed to evaluate how certain adolescents with externalizing symptoms may transition to developing substance use disorders.

Research suggests that the PR target may capture attention to a greater degree than the PU target due to the effect of reward conditioning on attention selection (Anderson et al., 2011; Bourgeois et al., 2015). We found that increases in externalizing and total psychopathology symptoms, as reported on the YSR, were associated with increased activation in the posterior cingulate cortex (PCC), the precuneus, and parietal regions when successfully inhibiting responses to PR relative to PU cues. The parietal cortex has been found to direct the allocation of attention (Shomstein and Yantis, 2006) and is involved in value-driven attention orienting (Anderson, 2019), while the precuneus and PCC have been associated with biasing towards salient stimuli (Rubia et al., 2009; Small et al., 2003). Age-related increases in posterior parietal activation during a rewarded anti-saccade task have been linked to externalizing symptoms, which was proposed to reflect developmental differences in orienting attention to reward-predicting cues (Quach et al., 2020). It may be that disrupted attention towards reward is a more general risk factor for psychopathology, not specific to externalizing psychopathology. These findings are consistent with previous studies suggesting that different forms of psychopathology are associated with differences in value-driven attentional capture (Sali et al., 2018; Anderson et al., 2017; Albertella et al., 2020). However, future research using a sample with more impaired functioning may be better suited to probe these findings.

We included associations with total psychopathology symptoms to evaluate whether a global measure of functioning was more informative

than dissociating unique variance associated with externalizing symptoms. Our analysis indicated that while activation in posterior regions of the brain while inhibiting to PR cues might be associated with psychopathology symptoms more generally, activation in the left MFG was selectively associated with externalizing symptoms. The specificity of these effects to inhibitory control over stimuli with a history of reward and not to response inhibition to PU stimuli suggests that the ability to regulate behavior to changing reward contingencies may be a useful marker for studying adolescent mental health.

4.1. Study limitations and future directions

The current study used a sample of typically developing adolescents to identify potential neural mechanisms related to symptoms of psychopathology. As a preliminary investigation into the relationship between inhibitory control over stimuli with a history of reward and psychological functioning during adolescence, the present study indicates that neural signaling when inhibiting previously rewarded behavior may predict individual differences in symptoms. However, the present findings should be considered in tandem with their limitations. Consistent with the currently popularized Research Domain Criteria (RDoC) framework (Insel et al., 2010), the present study conceptualized psychopathology as a continuum whereby normative processes become increasingly disrupted in psychopathology. However, the RDoC framework does not assume a continuous or linear relationship between neuronal function and psychopathology symptoms. Here, because the sample was typically developing, there was low overall variance in psychopathology symptoms, meaning that we may not have been able to adequately detect relationships with behavioral measures of the task or with neural activation to inhibitory control cues with no history of

reward. In conjunction with low variance in symptoms, our sample size may limit statistical power. Critically, future research should understand how these associations may change at higher levels of psychopathology with a larger sample of subjects. Convergent peer, parent, and self-reports may also be useful to characterize symptoms.

Another limitation of the current research was a relatively small number of No-Go trials across runs ($n = 96$ across three runs). Although externalizing psychopathology has been associated with persistent effects of reward conditioning on responses to stimuli (Gatzke-Kopp et al., 2009; Byrd et al., 2014), a low number of No-Go trials meant that we did not have sufficient power to model trials or blocks in our imaging data. Future studies assessing inhibitory control over stimuli with a history of reward would benefit from including a greater number of No-Go trials to assess how symptoms relate to changes in brain activation across trials and runs.

Finally, understanding whether underlying mechanisms of behavior may predict risk for the development of psychopathology is critical to informing preventative interventions. As a cross-sectional study, the present study is limited in its ability to infer how age-related changes in reward learning and inhibition impact risk for psychopathology. Rather, tracking changes in the ability to inhibit previously rewarded behavior across time would better evaluate whether developmental changes in this domain precedes changes in psychopathology symptoms. Thus, future research should leverage longitudinal designs to establish a temporal relationship between the interaction of inhibitory control and reward learning across adolescence and psychopathology symptoms.

4.2. Conclusion

The present investigation was novel in linking individual differences in adolescent psychopathology symptoms to neural recruitment when inhibiting a previously rewarded behavior. We observed a selective association between frontal recruitment and adolescent externalizing symptoms, which remained significant after controlling for internalizing symptoms. These results indicate that disruption in the executive control system may be critical to understanding the emergence of externalizing symptoms through its effect on reward learning and inhibition during adolescence. Our findings lay the foundation for future lines of inquiry into how reward history and cognitive control interact and predict risk for psychopathology during a crucial period of development.

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Declaration of Competing Interests

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

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