Development of Prefrontal Cortical Connectivity and the Enduring Effect of Learned Value on Cognitive Control

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Abstract

■ Inhibitory control, the capacity to suppress an inappropriate response, is a process employed for guiding action selection in the service of goal-directed behavior. Under neutral circumstances, inhibitory control success improves from childhood to adulthood and has been associated with developmental shifts in functional activation and connectivity of the PFC. However, the ability to exercise inhibitory control is challenged in certain contexts by including appetitive cues, a phenomenon that may be particularly pronounced in youths. Here, we examine the magnitude and temporal persistence of learned value's influence on inhibitory control in a cross-sectional sample of 8- to 25-year-olds. Participants first underwent conditioning of a motor approach response to two initially neutral cues, with one cue reinforced with monetary reward and the other with no monetary outcome. Subsequently, during fMRI, participants reencountered these cues as no-go targets in a nonreinforced go/no-go paradigm. Although the influence of learned value increasingly disrupted inhibitory control with increasing age, in young adults this pattern remitted over the course of the task, whereas during adolescence the impairing effect of reward history persisted. Successful no-go performance to the previously rewarded target was related to greater recruitment of the right inferior frontal gyrus and age-related increase in functional connectivity between the inferior frontal gyrus and the ventromedial PFC for the previously rewarded no-go target over the control target. Together, results indicate the complex influence of value on goals over development relies upon the increased coordination of distinct higher-order regions in the PFC. ■

INTRODUCTION

Adolescence is a period during which foundational development occurs for cognitive processes that contribute to goal-directed behavior in adulthood (Hartley & Somerville, 2015). Important among these maturing abilities is the development of cognitive control (Diamond, 2002), a collection of processes that support the selection and execution of actions toward achieving external goals (Aron, Robbins, & Poldrack, 2014). In daily life, cognitive control demands rarely occur in response to completely neutral stimuli. Rather, cues encountered in the real world typically have acquired some form of value based on previous experiences with them. It is thus a central challenge to goal-directed behavior to determine whether (or not) to allow learned value to shape future encounters with a stimulus. In this study, we probe the developmental mechanisms that underlie the resolution of this challenge. Participants first learned to link positive value with approaching a stimulus and then reencountered that stimulus in a new context in which they must execute the opposite action (withhold approach). We sought to trace age-related changes in the degree to which learned value history transfers to a new context to facilitate or impede subsequent goal-directed action, the temporal persistence of learned value history, and the underlying neurodevelopmental mechanisms of the influence of learned value on inhibitory processes.

Previous neurodevelopmental research has suggested that inhibitory control, a subclass of cognitive control defined as the ability to withhold a previously prepotent motor response, continues to improve throughout childhood and adolescence and into early adulthood. Engagement of the ventral lateral PFC, including the inferior frontal gyrus (IFG), plays a focal role in supporting the capacity for inhibitory control in adults (for a review, see Aron et al., 2014), and age-related changes in the recruitment of the IFG reflects age-related behavioral improvement in paradigms that measure inhibitory control in children and adolescents (Rubia et al., 2013; Somerville, Hare, & Casey, 2011; Durston et al., 2006).

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The interest in the development of the interplay between value and inhibitory control is not new; previous research has assessed the degree to which inhibitory control is differentially challenged by appetitive cues in childhood, adolescence, and young adulthood. For example, adolescents' inhibitory control is selectively disrupted when the targets of control are emotional faces (Dreyfuss et al., 2014; Somerville et al., 2011; Hare et al., 2008). These studies have demonstrated that activation in subcortical brain regions such as the ventral striatum respond to valenced affective cues and interact with signals in the lateral PFC and parallel selective behavioral reductions in inhibitory control (Somerville et al., 2011). Though previous studies have shown that an appetitive cue can interfere with inhibitory control, they confound active processing of the affective stimuli during inhibitory control. Critically, here we form a value association through conditioning, but test inhibitory control in the absence of continued reward delivery. Thus, we remove the simultaneous dual processing feature inherent in these other paradigms.

The influence of reinforcement history on performance has been studied in a limited way in developmental populations. Young children, 4–12 years old, have shown improved inhibitory control from a learned reward association (Winter & Sheridan, 2014), potentially because young children use the increased salience induced by reinforcement history to facilitate control behavior (Chevalier, Chatham, & Munakata, 2014). In contrast, 13- to 16-year-old adolescents have exhibited the opposite pattern, whereby reward history increased attentional capture but led to disruptions in goal-directed behavior rather than facilitating it, an effect that persisted longer in time in adolescents than in adults (Roper, Vecera, & Vaidya, 2014). Together, these studies offer the intriguing possibility that, in the transition from childhood to adolescence, learned value history shifts from facilitating to intruding on subsequent goal-directed behavior.

Although the flexible transfer of learned value can benefit goal-directed behaviors, it can also be detrimental when novel environmental demands are in conflict with previous learning. In this study, we deliberately created such a conflict, crossing action and reward demands across consecutive tasks, to ask whether learned value history has differential effects on subsequent inhibitory control over development. Moreover, we examine the durability of influence of value history by investigating the degree to which value intrusion on inhibitory control persists over time. We interrogate these processes in a two-part paradigm where participants first learned to associate a motor action with value in response to an arbitrary cue and tested the degree to which this value history subsequently influences inhibitory control during fMRI. Broadly, this work aims to identify the neurodevelopmental processes that differentially support value history and inhibitory control interactions across development.

METHODS

Participants

One hundred forty-six 8- to 25-year-olds participated in the study. Participants were recruited from the community using online (e.g., Craigslist) and print advertisements (e.g., on public transit) and flyers. Individuals were excluded from participation for self- or parent-reported history of neurological disorders, head trauma, diagnosis of any psychological or learning disorder, having a native language other than English, and having MRI contraindications. The demographic composition of the sample reflected the greater Boston area with respect to ethnicity (18% Hispanic, 77% Non-Hispanic, 5% unreported) and race (14% Asian, 14% Black, 58% White, 1% Native American/Alaskan Native, 6% biracial, 7% unreported).

Some participants were excluded from final analyses because of task performance or imaging data quality concerns. Loss of two runs (of three total) resulted in exclusion. Noncompliance with go/no-go behavioral task instructions was defined as go accuracy less than 50% and/or no-go accuracy less than 25%. Thresholds were selected to ensure minimum command of the task (i.e., understanding when to press and when not to press) without penalizing individuals with lower accuracy due to legitimate challenge. Seventeen participants were excluded (mean [M] age of excluded participants = 11.6 years, range = 8–19 years); $n = 9$ for task noncompliance (mean = 12.5 years, range = 9–19 years), $n = 5$ for motion during fMRI (mean = 9.9 years, range = 8–11 years; see fMRI General Linear Model Estimation: Task Effects and Motion for censoring criterion), and $n = 3$ for a combination of both (mean = 12.1 years, range = 8–13 years). Two additional participants did not complete the study: one due to discomfort in the scanner (age = 12.2 years) and one due to technical issues (age = 9.1 years). We administered the Matrix Reasoning Scale of the Wechsler Abbreviated Scale of Intelligence (Second Edition; data missing for four participants) to estimate intellectual ability. There was no significant difference in Matrix Reasoning scaled score, $t = -1.6$, degrees of freedom (df) = 140, $p = .11$, between individuals that were retained for analyses versus excluded from analysis, suggesting that excluding participants for data quality did not otherwise bias the sample.

The final sample consisted of 127 individuals (N_{female} = 65, age range = 8.09–25.79 years, mean age = 16.13 years, $SD = 4.77$). The distribution of male and female sex was not related to age (sex by age Pearson's correlation, $r = .09$, $df = 125$, $p = .33$). There was no significant relationship between age and scaled Matrix Reasoning score, $r = -.06$, $df = 121$, $p = .52$, implying participant age was not confounded with age-normed intellectual ability.

All adult participants provided informed consent to participate in the study; all child and adolescent

participants provided informed assent, and a parent or legal guardian provided permission to participate and informed consent. Participants and their parents were remunerated for their time. All procedures were approved by the Partners Human Research Committee institutional review board at Massachusetts General Hospital/Harvard Medical School.

Task Overview

The conditioned appetitive response inhibition task (CARIT; adapted from Winter & Sheridan, 2014) is a two-phase task with an initial reward conditioning phase and a subsequent test of inhibitory control over previously conditioned stimuli (Figure 1). In the first phase, reward is conditioned to a neutral stimulus in a modified monetary incentive delay task (Knutson, Westdorp, Kaiser, & Hommer, 2000), and an acquired reward-related approach tendency is confirmed by measuring increased response speeding to the reward-related cue. In the second phase, the reward-associated stimulus and an unrewarded control stimulus are carried forward to an inhibitory control task in which they are no-go stimuli. The second phase was administered approximately 1 hr after the first phase. Inhibitory control is measured by successful no-go task performance; of interest is the difference in no-go task performance for the previously rewarded compared with the control stimulus. All behavioral tasks were presented in E-Prime Version 2.0 (Psychology Software Tools).

CARIT: Conditioning Phase

Participants completed the first study phase seated in a quiet room. Participants acquire conditioned appetitive responses to initially neutral stimuli through repeated pairing of a rapid button press and a monetary gain. Two shapes, a circle and a triangle, underwent conditioning; which shape was rewarded was counterbalanced across participants. The nonrewarded shape, for example, the circle, was never associated with a monetary outcome (no reward); all responses resulted in $0. The rewarded shape, for example, the triangle, was associated with a monetary gain (high reward); if the participant correctly pressed during a short response window, there was a 70% chance of winning $0.50 and a 30% chance of winning $5.00, but responses that were too slow resulted in $0. 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 second phase of the task and are not analyzed here. There were 156 total trials with 39 each of the four shapes presented intermixed pseudorandomly.

In a trial (Figure 1A), participants saw a black line drawing of a shape (500 msec) against a white background followed by a white fixation cross against a black background (jittered time interval, 2000–2375 msec, M = 2187.5 msec, SD = 140.2 msec); this change in background color signaled the participant to prepare to make a very rapid button press. Following the jittered fixation, a white line drawing of the previously cued shape appeared against the black background, and participants were instructed to press a button very quickly to obtain the outcome. Immediately following, feedback indicated if the response was sufficiently rapid and the resulting monetary outcome (1500 msec).

The response window adjusted dynamically during the task to control for response accuracy and hence exposure

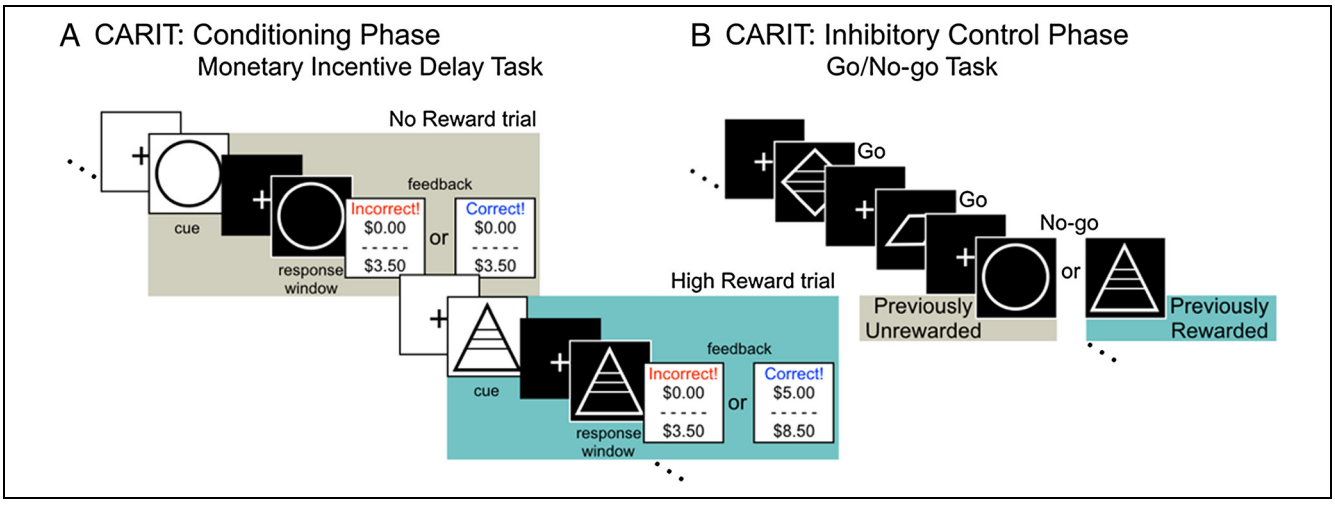

Figure 1. CARIT. (A) Neutral cues are conditioned to have an equivalent associated motor history with differential reward history. One cue is reinforced with reward, and another cue is never rewarded. A feedback screen shows participants if the response was fast enough, the amount earned on the trial, and the cumulative amount earned in the block. (B) Conditioned cues become no-go targets in the following inhibitory control task to measure the differential impact from conditioning history on inhibitory control processes. There are no rewards in the go/no-go task.

to reinforcement per stimulus per individual. A staircase algorithm adjusted the response window for each stimulus separately to set performance to 66% accuracy by lengthening the correct response window for a stimulus if the accuracy was too low and shortening it if the accuracy was too high. The duration of the response window at the start of the task was determined by the average RT from a practice round immediately preceding the task.

After completing the conditioning task, we collected self-report ratings of the subjective importance of each shape on a 5-point Likert scale to verify that the repeated exposure to the different shape–outcome pairings resulted in intended changes to the subjective value of the shapes, specifically whether the high-reward shape would have greater subjective importance than the no-reward shape. The posttest assessment was not collected in one adult participant ($n = 126$). Participants were paid the total amount earned in cash immediately following the self-report ratings.

CARIT: Inhibitory Control Phase

The second phase of the task, which was administered during fMRI scanning, measured the degree to which the reward history acquired in the conditioning phase influenced subsequent inhibitory control and associated neural processes. Only the high-reward and no-reward stimuli from the previous conditioning phase were carried forward to the inhibitory control phase, which we will refer to as the "previously rewarded" (PR_no-go) and "previously unrewarded" (PU_no-go) targets. Critically, in the go/no-go task, these targets are no longer signaling reward; there are no incentives and no bonus payments for the go/no-go task, which was explicitly stated to the participants.

In the go/no-go task (Figure 1B), participants were instructed to respond by pressing a button as rapidly as possible to a category of targets that appear frequently (go targets, 264 trials total) but were instructed to withhold their button press to a category of targets that appear occasionally (no-go targets). Go stimuli were line drawings of novel shapes that had not previously appeared in the conditioning phase. The two no-go targets PR_no-go and PU_no-go were each presented on 48 trials (96 trials total). The order of presentation for all the targets was pseudorandomized.

We employed a rapid event-related design where go and no-go target stimuli were presented for 600 msec, followed by a jittered fixation interstimulus interval ranging from 500 to 4500 msec ($M = 1875$ msec, $SD = 1221$ msec). Correct and incorrect responses were recorded during a 1100-msec response window beginning at the onset of the target. Participants viewed the task projected onto a screen in a mirror mounted on the head coil and used an MR-compatible button box to make behavioral responses.

Behavioral Analysis

Analysis of behavioral measures focused on the main effects of the task variables and interactions between task variables and participant age, using linear mixed-effects models (Pinheiro, Bates, DebRoy, Sarkar, & R Core Team, 2018); we report unstandardized beta (B) coefficients. Statistical analyses were performed in R.

Age

Participant age was modeled as a continuous variable to avoid parsing the sample at presumed boundaries to create age groups (Somerville, 2016). For modeling changes that steadily increase or decrease with age, we applied a mean-centered linear age predictor. Because of previous work showing nonlinear trajectories of affective influences on cognitive processes (Somerville et al., 2011), we also evaluated a quadratic age model to test for "U" or inverted-U-shaped changes with age, created using a squared mean centered age term. To evaluate the benefit of including the linear and quadratic age terms for explaining variability in a dependent measure, we used the Akaike information criterion (AIC; Akaike, 1974), where evidence for a model with better explanatory power is determined by the lowest AIC score. We compared model fits by a likelihood ratio chi-square test for three nested models: a model without age, a model with main effect and interactions with only linear age, and a model with linear and quadratic age predictors and interactions with task variables.

Conditioning Phase

Task outcomes of interest were RT, response accuracy, and importance ratings of the stimuli at the end of conditioning. We confirmed the effectiveness of the reward conditioning manipulation by assessing whether conditioning induced greater response invigoration (i.e., RT speeding) to the high-reward compared with no-reward cue and by evaluating participants' subjective perceptions of the conditioned cues evidenced by posttest ratings. The difference in RT speeding was also used in analysis of the inhibitory control task to assess the degree to which differential response invigoration could explain inhibitory control differences between the previously rewarded and previously unrewarded targets. In addition, we confirmed that the staircase procedure correctly matched proportion of accuracy across cues for participants. Finally, for each outcome (RT, subjective rating, and accuracy), we examined the interaction between reward conditioning on these variables and age. For each outcome variable, the linear mixed-effects model contained fixed-effect predictors for reward condition, linear age, quadratic age, interactions between reward condition and age (linear and quadratic), and a random effect parameter for participant.

Inhibitory Control Phase

The inhibitory control phase was designed to test whether inhibitory control was influenced by the acquired reward history, with the outcome of interest being successfully withheld responses to no-go targets (i.e., no-go accuracy). We conducted a linear mixed-effects model for no-go accuracy with fixed-effect factors of reward history (PR_no-go vs. PU_no-go), time since conditioning (Run 1, Run 2, Run 3), age (linear and quadratic), and interactions between reward history, time, and age, modeling participant as a random effect. To assess whether the degree of response invigoration during conditioning additionally impacted later inhibitory control or better accounted for behavioral differences in inhibitory control rather than reward history, motor history (i.e., RT to high reward vs. no reward cues) was added as a fixed-effect term for mixed-effects modeling.

To assess general main effects of task performance with age, we conducted a linear mixed-effects model for accuracy with a fixed-effect parameter for action type (go vs. no-go collapsed over reward history) and their modulation by age, with a random effect for participant. This general analysis comparing go and no-go accuracy allowed for comparative inference to previous work using go/no-go paradigms.

MRI Acquisition

Images were acquired at the MGH/HST Athinoula A. Martinos Center for Biomedical Imaging on a 3T CONNECTOM scanner (Fan et al., 2016; Setsompop et al., 2013) using a custom-made 64-channel phased array head coil (Keil et al., 2013). Functional BOLD images were collected in three runs of 124 volumes (total of 372 volumes) of interleaved descending T2*-weighted echo-planar (EPI) volumes at oblique transverse orientation with the following acquisition parameters: repetition time = 2500 msec, echo time = 30 msec, flip angle = 90°, array = 72 × 72, 39 slices, effective voxel resolution = 3.0 mm^3, field of view = 216 mm. A high-resolution T1-weighted multiecho magnetization-prepared rapid gradient-echo (MEMPRAGE; van der Kouwe, Benner, Salat, & Fischl, 2008) image, accelerated with generalized autocalibrating partially parallel acquisitions (Griswold et al., 2002) was acquired for registration purposes with the following acquisition parameters: repetition time = 2530 msec, echo time = 1.61 msec, flip angle = 7°, array = 256 × 256, 208 slices, voxel resolution = 1.0 mm^3, field of view = 256 mm.

Preprocessing

Brain imaging data processing and statistical analysis were performed in FMRIB's Software Library (FSL; Jenkinson, Beckmann, Behrens, Woolrich, & Smith, 2012). The MEMPRAGE image was skull-stripped using the Brain Extraction Tool (Smith, 2002), segmented into probabilistic tissue maps of gray matter, white matter, and cerebrospinal fluid using FMRIB's Automated Segmentation Tool (Zhang, Brady, & Smith, 2001), and registration matrices were estimated for transformation into standard template space (Montreal Neurological Institute [MNI] template, voxel dimensions 2 mm^3).

Functional images were reconstructed, intensity-normalized, and then preprocessed using the fMRI Expert Analysis Tool (FEAT, v.6). Functional images were slice time-corrected using Fourier space time-series phase-shifting. Realignment estimates for correcting motion in three translational and three rotational directions were computed in MCFLIRT (Jenkinson, Bannister, Brady, & Smith, 2002), and functional images were realigned. The skull was stripped using the Brain Extraction Tool. Spatial smoothing was applied using a Gaussian kernel of 5 mm FWHM. Images underwent high-pass temporal filtering (Gaussian-weighted least squares straight line fitting, with sigma = 50.0 sec) and grand mean intensity normalization. The images from each scanning run were coregistered to the participant's anatomical image, and registration matrices were estimated for later linear transformation to a standard template (T1 MNI template, voxel dimensions 2 mm^3) using FLIRT (Jenkinson et al., 2002; Jenkinson & Smith, 2001).

fMRI General Linear Model Estimation: Task Effects and Motion

We used a general linear model (GLM) to estimate effects of task and control for effects of noninterest. The GLM design for task events included onsets and durations for PR_no-go trials correct nonresponses, PU_no-go trials correct nonresponses, PR_no-go trials false alarms, PU_no-go trials false alarms, go trials correct responses, and go trials missed responses. All task regressors were convolved with the canonical hemodynamic response function. For analysis of reward history manipulation (PR_no-go vs. PU_no-go), we created a GLM as described but composed of only the two successfully inhibited no-go regressors with all other events modeled in a single regressor of noninterest for maximization of power and reduced loss of degrees of freedom for events of noninterest to the current report.

Nuisance regressors consisted of rigid body (three translational and three rotational) estimates of motion from realignment during preprocessing, their derivate, their square, and the square of the derivate. The rigid body estimates of motion were submitted to Art software (http://gablab.mit.edu/index.php/software) implemented through Nipype (Gorgolewski et al., 2011) to identify time points 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. Runs were excluded if they included a single relative

movement greater than 5 mm or 15% time points censored from motion and artifact detection.

fMRI GLM Estimation: Task-based Functional Connectivity

A GLM was constructed for each participant to identify voxels that coactivated with the IFG more during PR_no-go compared with PU_no-go trials for different ages using psychophysiological interaction (PPI; O'Reilly, Woolrich, Behrens, Smith, & Johansen-Berg, 2012; Friston, 2001). The psychological regressor consisted of onsets and durations for all correct no-go trials with a weight of 1 for PR_no-go and −1 for PU_no-go events. For the physiological regressor, we extracted the time series from a 3-mm sphere in the IFG around the peak ($x = 54$, $y = 20$, $z = -2$) of an activation observed in a separate group analysis (see Results). Signal was extracted from this seed from the preprocessed functional time series. The GLM was composed of event onsets and durations for the psychological regressor, the physiological regressor, and the interaction term of the psychological and physiological regressors computed within FEAT and nuisance regressors for motion and censoring parameters described above, as well as ventricular and white matter signal time series. These time series are effective at controlling for spurious connectivity results that can arise from time series based analyses (Satterthwaite et al., 2013).

fMRI Group-Level Statistical Analysis

Group-level mixed-effect statistical analyses were implemented in FEAT with FLAME1 (Eklund, Nichols, & Knutsson, 2016; Woolrich, Behrens, Beckmann, Jenkinson, & Smith, 2004). The analysis of functional images focused on the main effects of go/no-go task event types and interactions between task event types and participant age (linear and quadratic age, mean-centered). All group-level results for activation and functional connectivity were thresholded using a voxel-wise Z statistic threshold $Z = 2.3$ and a cluster threshold $p = .05$ for a family-wise error correction of FWE-$p < .05$.

For the main effects of action (go vs. no-go collapsed over reward history) and its modulation by age, fixed-effect level contrasts for each participant were modeled in a group-level GLM for go > no-go and for no-go > go, with age included as a covariate of interest. Analysis of functional connectivity followed the same logic for the interaction contrast.

To test for the influence of the reward history manipulation on inhibitory control in the brain, we constructed a group-level GLM for PR_no-go > PU_no-go and for PU_no-go > PR_no-go, with age included as a covariate of interest. This analysis was conducted within a functionally defined mask of voxels active in the no-go > go contrast in the full sample (with no age covariate). The purpose of the masked analysis was to constrain the spatial search space to increase the power to detect group-level and age-related differences in the subtler manipulation of reward history. The results were thresholded using the same voxel-wise Z statistic threshold $Z = 2.3$ and a cluster threshold $p = .05$ for a correction of FWE-$p < .05$ within the mask. We also conducted an exploratory whole-brain analysis of the reward history manipulation and its modulation by age using a voxel-wise Z statistic threshold $Z = 2.3$ and a cluster threshold $p = .05$ for the whole brain (see results on Open Science Framework: https://osf.io/re7jt).

For display purposes, activation parameter estimates for each participant were extracted from a 3-mm^3 sphere drawn around the activation peak using featquery, and values were converted into percent signal change. For large spatially distributed results, local maxima within a significant cluster were determined by FSL's cluster utility tool with a 4-mm minimum spatial distance, and only the highest Z statistic within an anatomical region was reported. Anatomical labels for cluster peaks and local maxima were identified using the cortical and subcortical Harvard–Oxford Probability Atlases.

RESULTS

Conditioning Phase

The staircase procedure resulted in similar overall performance accuracy for the high-reward and no-reward cues, but there was a trend in the direction of higher accuracy for the high-reward cue (high reward: $M = 0.659$, $SEM = 0.002$; no reward: $M = 0.652$, $SEM = 0.003$; unstandardized beta coefficient (B) = −.007, $df = 126$, $p = .061$). For overall performance accuracy, the addition of the linear or quadratic age did not improve model fit over the reward condition term alone ($AIC_{No\_age} = -1079.4$, $AIC_{Linear} = -1076.0$, no age model vs. linear age model likelihood ratio test chi-square (χ^2) = 0.54, $df = 2$, $p = .77$, $AIC_{Quadratic} = -1072.3$, linear age model vs. quadratic age model $\chi^2 = 0.31$, $df = 2$, $p = .86$). Thus, the best-fit model for accuracy did not include any age terms or their interactions, implying that the staircase procedure worked comparably across all ages. This provides confidence that the conditioning phase yielded comparable frequency of reinforcement across the sample age range.

As expected, RT was significantly faster for the high-reward ($M = 217.3$ msec, $SD = 44.7$) than the no-reward cue ($M = 228.7$ msec, $SD = 35.9$; $B = 8.0$, $df = 124$, $p = .0003$). This finding confirms the conditioning phase of the experiment induced an acquired approach response that was greater for the high-reward condition relative to the no-reward condition. For RT, the model that included quadratic age yielded the best fit ($AIC_{No\_age} = 2259.3$, $AIC_{Linear} = 2228.5$, $AIC_{Quadratic} = 2218.8$, no age model vs. linear age model $\chi^2 = 34.76$, $df = 2$, $p < .0001$, linear age model vs. quadratic age model $\chi^2 = 13.7$, $df = 2$, $p = .001$), and therefore, both linear and quadratic age effects

are reported here. There was an overall effect of age on RT such that RTs in general decreased with increasing age and showed a local minimum around late adolescence when responses were the fastest (linear age: $B = -2.99$, $df = 124$, $p < .0001$; quadratic age: $B = 0.320$, $df = 124$, $p = .0004$). However, there was no interaction between age and reward condition on RT (reward interaction with linear age: $B = 0.27$, $df = 124$, $p = .41$; reward interaction with quadratic age: $B = -0.05$, $df = 124$, $p = .48$), demonstrating that the observed relative speeding for the high-reward cue was acquired similarly across all ages.

For posttask self-report ratings of importance, participants interpreted the high-reward cue ($M = 4.60$, $SEM = 0.07$) to be more important when compared with the no-reward cue ($M = 1.85$, $SEM = 0.09$; $B = -2.76$, $df = 124$, $p < .0001$). The addition of linear and quadratic age did not improve model fit ($AIC_{No\_age} = 681.0$, $AIC_{Linear} = 682.9$, $AIC_{Quadratic} = 686.6$, no age model vs. linear age model $\chi^2 = 2.1$, $df = 2$, $p = .36$, linear age model vs. quadratic age model $\chi^2 = 0.31$, $df = 2$, $p = .86$), supporting that subjective assessment of the shape cues was consistent across the age range. Together, these results show successful conditioning of a reward association to an initially neutral cue, resulting in two cues with equivalent learning and previous motor experience, but a differential reward association that was consistent across the age range.

Reward History Influence on Inhibitory Control over Development

As expected, based on past work using the go/no-go task, participants were significantly more accurate to go ($M = 0.97$, $SEM = 0.006$) than no-go trials ($M = 0.61$, $SEM = 0.014$; $B = -0.36$, $df = 125$, $p < .0001$). For overall go and no-go accuracy, the inclusion of linear age significantly improved model fit ($AIC_{No\_age} = -339.9$, $AIC_{Linear} = -387.2$, no age model vs. linear age model $\chi^2 = 51.3$, $df = 2$, $p < .0001$), but the addition of quadratic age did not ($AIC_{Quadratic} = -383.8$, linear age model vs. quadratic age model $\chi^2 = 0.64$, $df = 2$, $p = .72$). Previous work has found that the general ability to exercise inhibitory control improves from childhood to adulthood, which we also observed here evidenced by an interaction between linear age and action type ($B = 0.014$, $df = 125$, $p < .0001$). Post hoc analyses of the interaction showed age-related performance improvements were more dramatic for no-go ($r = .46$, $df = 125$, $p < .0001$) than go ($r = .14$, $df = 125$, $p = .11$) targets (Fisher Z-transformed correlation coefficient comparison, $Z = 2.83$, $p = .005$). We did not observe a main effect of age on overall accuracy ($B = 0.002$, $df = 125$, $p = .38$). Having found that inhibitory control performance improves with age, we turned to the key behavioral test of whether differential reward conditioning history (PR_no-go vs. PU_no-go) influenced subsequent inhibitory control processes and for age differences in no-go performance as a function of reward history and time since conditioning.

For no-go accuracy by previous conditioning, the inclusion of quadratic age significantly improved model fit over the model with only reward history and time ($AIC_{No\_age} = -688.7$, $AIC_{Linear} = -722.1$, $AIC_{Quadratic} = -729.4$, no age model vs. linear age model $\chi^2 = 45.4$, $df = 6$, $p < .0001$, linear age model vs. quadratic age model $\chi^2 = 19.3$, $df = 6$, $p = .004$). There was a significant reduction of successful inhibitory control for the PR_no-go target ($M = 0.59$, $SEM = 0.02$), compared with the PU_no-go target ($M = 0.62$, $SEM = 0.02$; $B = -0.04$, $df = 590$, $p = .009$; Figure 2A), showing that previous reward conditioning impairs inhibitory control. This main effect of reward history on no-go accuracy was qualified by a trend interaction with linear age ($B = -0.006$, $df = 590$, $p = .064$, Figure 2B) but did not interact with quadratic age ($B = -0.0001$, $df = 590$, $p = .88$). Exploratory post hoc tests showed a positive association between age and no-go accuracy for the PU_no-go target ($r = .44$, $df = 125$, $p < .0001$) and a positive association for the PR_no-go target ($r = .28$, $df = 125$, $p < .0001$). These positive associations significantly differed ($Z = 2.11$, $p = .035$), with a stronger age association for the PU_no-go target. The youngest participants showed slightly improved inhibitory control for the PR_no-go target relative to PU_no-go target. However, this pattern reversed such that reward history began to have an impairing effect on no-go accuracy in early adolescence, a pattern that intensified into early adulthood.

There was a significant effect of time since conditioning on no-go accuracy ($B = -0.082$, $df = 590$, $p < .0001$) that did not interact with reward history alone ($B = 0.034$, $df = 590$, $p = .12$) but did interact with reward history and quadratic age ($B = -0.003$, $df = 590$, $p = .007$). To investigate this three-way interaction, we fit models for no-go accuracy by reward history and age for each third of the task (Run 1, Run 2, Run 3). The first two runs were best fit by models that included linear age (Table 1, Figure 2C) with a trend toward a significant interaction between reward history and linear age in the first run ($B = -0.006$, $df = 125$, $p = .064$) and a significant interaction between reward history and linear age in the second run ($B = -0.009$, $df = 122$, $p = .012$), whereas the last run was best fit by the model that included quadratic age, with a significant interaction between reward history and quadratic age ($B = -0.003$, $df = 112$, $p = .0001$). This showed that, for the earlier parts of the task, the intrusion from previous reward conditioning on inhibitory control increased with age. However, by the end of the task, the oldest participants had recovered from the previous conditioning, but in older adolescent participants, the impairment to inhibitory control from previous conditioning persisted.

Finally, to evaluate whether the conditioned motor approach additionally interfered with later inhibitory control success, we tested for improvement in the

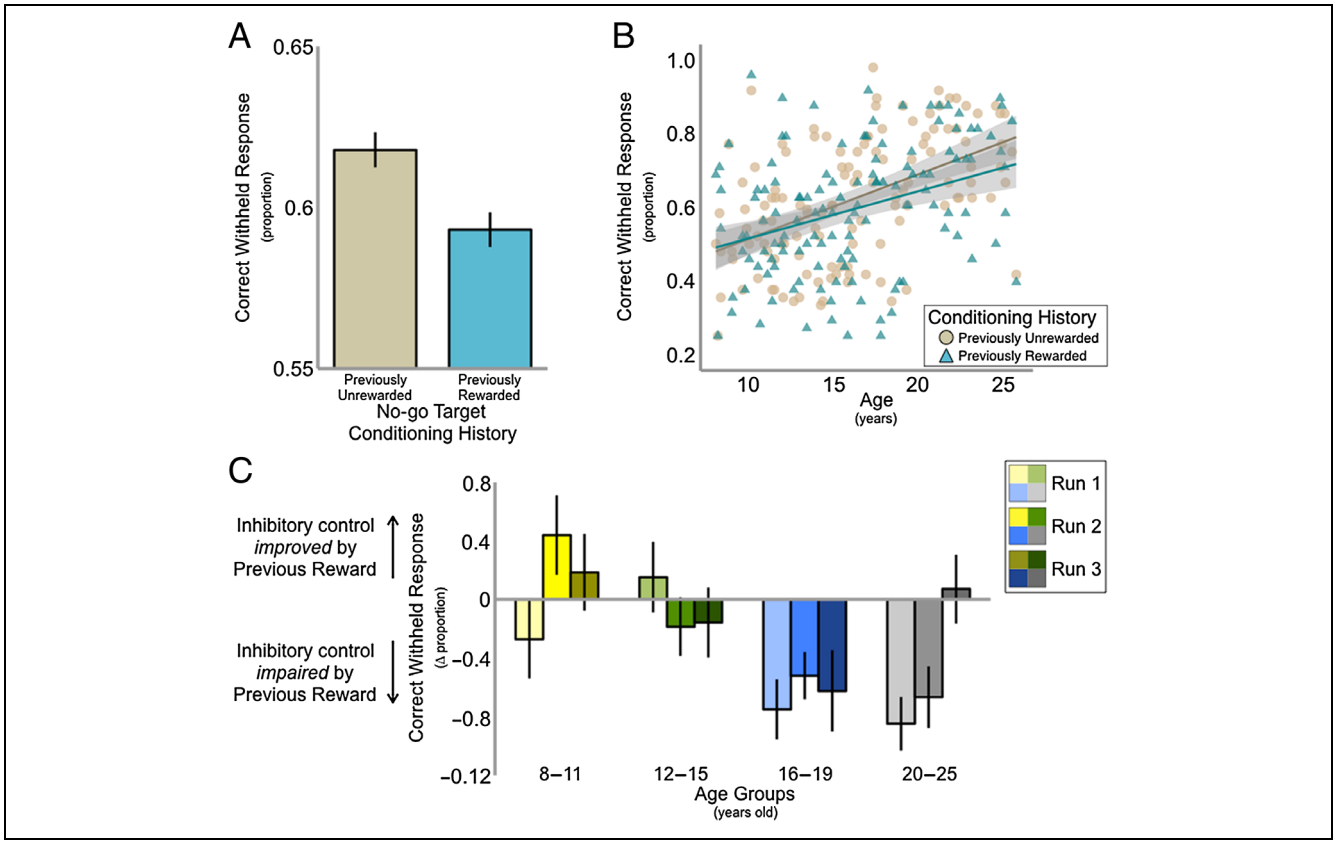

Figure 2. Reward conditioning history impairs inhibitory control differentially over development. (A) Reward history impairs inhibitory control, even in the absence of continued reward delivery. Error bars show ± 1 *SEM*, within participants for repeated measure. (B) Impairment in inhibitory control from reward history begins to emerge in adolescence and grows greater as age increases. Points show individual participant data. Shading around fit lines shows between participants ± 1 *SEM*. (C) Difference score between proportion successful inhibitory control for the previously unrewarded versus previously rewarded no-go target within participants for each functional imaging run. Inhibitory control is most impaired from conditioning history in the older participants early in the task. However, by the end of the task, among these older individuals impairment persists in the adolescents. Plotted by grouped ages for display purposes only. Error bars show ± 1 *SEM*, within participants for repeated measure.

mixed-effect model fit if motor history was substituted for reward history or if it was added to the reward history model. Reward history better accounted for performance than including motor history (reward history model AIC = −729.4; motor history model AIC = −700.8; reward–motor interaction model AIC = −712.3; reward history vs. reward–motor interaction model, $\chi^2 = 18.9$, $df = 18$, $p = .40$; motor history vs. reward–motor interaction model, $\chi^2 = 47.4$, $df = 18$, $p = .0002$). This suggests that the influence of reward history better explains

Table 1. Mixed-effect Model Comparison (Likelihood Ratio Chi-square Test) for Behavioral Interaction between Reward History, Age, and Time since Conditioning

Time Point	*Model*	*AIC*	*Comparison*	χ^2	*p*
Run 1	No age	−179.6			
	Linear	−201.5	No age vs. linear	25.9	<.0001
	Quadratic	−197.6	Linear vs. quadratic	.11	.94
Run 2	No age	−144.2			
	Linear	−163.0	No age vs. linear	22.8	<.0001
	Quadratic	−162.4	Linear vs. quadratic	3.4	.19
Run 3	No age	−128.8			
	Linear	−154.7	No age vs. linear	29.9	<.0001
	Quadratic	−166.3	Linear vs. quadratic	15.5	.0004

Table 2. Contrasts of Correctly Executed Action Covaried by Participant's Age (Whole Brain), Threshold FWE-$p < .05$

				MNI Coordinate			
Harvard–Oxford Atlas Label	*Voxels*	*p Cluster*	*Z Score*	*X*	*Y*	*Z*	
Linear Age × No-go > Go							
R. temporo-occipital middle temporal gyrus	1022	.000492	4.01	58	−52	−2	Cluster 1 peak
R. temporo-occipital inferior temporal gyrus			3.86	50	−48	−6	Local max
R. angular gyrus			3.72	56	−52	20	Local max
R. posterior superior temporal gyrus			3.61	66	−30	6	Local max
R. inferior lateral occipital cortex			3.3	54	−62	10	Local max
R. posterior middle temporal gyrus			3.02	62	−36	0	Local max
R. middle frontal gyrus	703	.00665	4.15	40	10	50	Cluster 2 peak
R. superior frontal gyrus			3.35	22	18	54	Local max
L. temporo-occipital inferior temporal gyrus	688	.00758	3.77	−42	−62	−8	Cluster 3 peak
L. temporo-occipital middle temporal gyrus			3.59	−62	−54	2	Local max
L. posterior middle temporal gyrus			3.31	−56	−42	−2	Local max
L. posterior superior temporal gyrus			2.87	−50	−38	4	Local max
L. posterior inferior temporal gyrus			2.58	−56	−42	−18	Local max
R. inferior frontal gyrus	594	.0176	3.64	52	26	−2	Cluster 4 peak
R. frontal pole			3.41	48	36	16	Local max
R temporal pole			3.4	50	22	−14	Local max
R frontal orbital cortex			3.19	52	24	−10	Local max
R. angular gyrus	545	.0277	3.92	42	−54	44	Cluster 5 peak
R. posterior supramarginal gyrus			3.58	54	−46	52	Local max
R. superior lateral occipital cortex			3.27	32	−80	34	Local max
Linear Age × Go > No-go, and Quadratic Age × No-go > Go							
No above threshold clusters observed							
Quadratic Age × Go > No-go							
L. postcentral gyrus	1160	.00017	4.17	−14	−40	60	Cluster 1 peak
L. supplementary motor cortex			3.81	−12	−6	52	Local max
L. superior frontal gyrus			3.60	−20	4	46	Local max
L. precentral gyrus			3.38	−30	−6	46	Local max
L. precuneus cortex			3.20	−12	−42	44	Local max
L. middle frontal gyrus			3.05	−28	8	48	Local max
L. superior parietal lobule			2.64	−16	−52	60	Local max
R. precuneus cortex			2.52	2	−44	48	Local max

the age-related differences in interrupting later inhibitory control and the effects over time.

fMRI Response to Go and No-go Trials

Whole-brain maps for overall go/no-go main effects exhibited activation patterns that are highly consistent with prior work on motor processes and inhibitory control. We observed significantly greater activity in the left motor cortex and left visual cortex for go > no-go trials (see https://osf.io/re7jt). When comparing no-go > go trials, we observed significantly greater responding in a broadly distributed set of brain regions including the bilateral insular cortex extending laterally into the IFG, the right precuneus, and regions of the basal ganglia.

When including participant age as a covariate of interest in the group-level GLM, for no-go > go, we found five significant clusters exhibiting age-related changes in activation magnitude, including the right IFG (rIFG; see Table 2; Figure 3A), which increased positively with increasing participant age (Figure 3B). There were no significant clusters for the go > no-go comparison.

Functional Activity and Connectivity Related to Conditioned Reward History

Key analyses examined neural responses, which differentiated between PR_no-go versus PU_no-go trials within a functional mask of voxels identified as more active for no-go > go. The comparison of PR_no-go > PU_no-go yielded two significant clusters: one in the rIFG (peak [$x = 54$, $y = 20$, $z = -2$], peak Z statistic = 4.03, 405 voxels; Figure 4A) and the other in the left occipital pole (peak [$x = -28$, $y = -92$, $z = -4$], peak Z statistic = 6.49, 689 voxels). Participant age did not significantly relate to levels of activation in these regions, suggesting this effect was developmentally invariant.

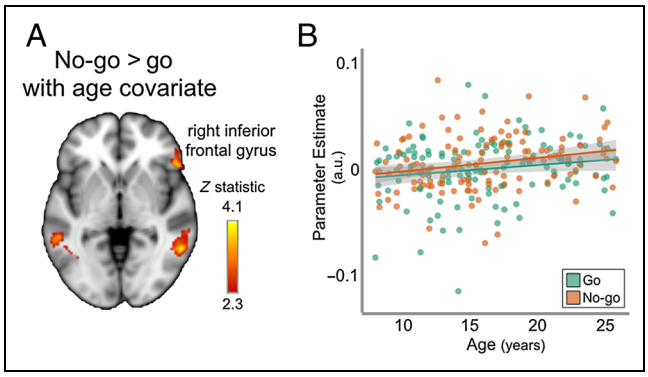

Figure 3. Age-related increases in brain activity associated with successful inhibitory control. (A) Areas with greater activation for no-go > go with increasing age, FWE-$p < .05$. Display at peak of rIFG cluster, $z = -2$. (B) For display purposes only, extracted values from the rIFG cluster for each participant. Green points show activation for the contrast of go > baseline, and orange points for the contrast of no-go > baseline. Shading around fit lines shows between participants ± 1 *SEM*. a.u. denotes arbitrary units.

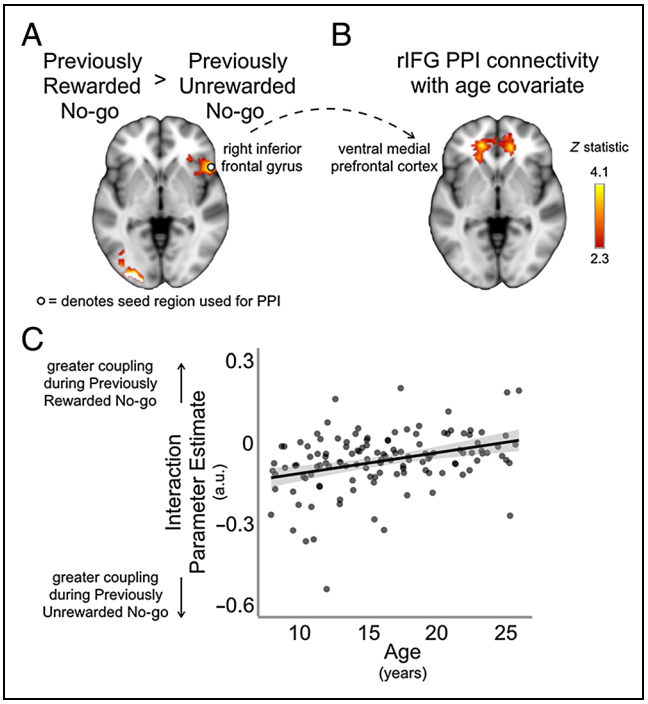

Figure 4. Brain activity and functional connectivity associated with interaction between successful inhibitory control (no-go), reward history, and development. (A) Within the areas functionally defined by the contrast of no-go > go, the rIFG was more active for successfully withheld previously rewarded > previously unrewarded no-go targets, FWE-$p < .05$. Display shows rIFG peak at $z = -2$. Peak of rIFG cluster was used as a seed for the physiological factor in the PPI analysis. (B) Result map of the interaction from the PPI analysis, FWE-$p < .05$. Display shows peak $z = -2$. (C) For display purposes, the interaction effect between increasing age and the interaction result from the PPI analysis. Shading around fit line shows between participants ± 1 *SEM*.

The opposite contrast of PU_no-go > PR_no-go showed no significant activations.

PPI connectivity analysis seeded in the rIFG at ($x = 54$, $y = 20$, $z = -2$) was conducted to identify differential functional connectivity for PR_no-go and PU_no-go targets by age. Results revealed an age-related shift in task-dependent coupling between the ventral medial PFC (vmPFC) extending bilaterally across the midline (peak [$x = -16$, $y = 42$, $z = -2$], peak Z statistic = 4.06, 484 voxels; Figure 4B) and the rIFG. To understand the direction of this age-related emergence of rIFG–vmPFC connectivity, we extracted the parameter estimate from the PPI interaction term for each participant (Figure 4C). We found that, as age increased, the coupling between rIFG–vmPFC shifted from being more coactive during PU_no-go targets toward being more coactive during PR_no-go targets.

DISCUSSION

This study examined age-related changes in the behavioral and neurodevelopmental processes that shape the influence of reward history on inhibitory control. Participants aged 8–25 years first learned to associate a

button response to an initially neutral stimulus with a monetary reward and subsequently were instructed to withhold a button press to that stimulus and a control stimulus during fMRI. Results demonstrated that, on average, reward history interfered with inhibitory control. This effect was qualified by an interaction with age, such that with increasing age, reward history increasingly intruded on inhibitory control. However, whereas the inhibitory control of individuals in the upper age range was generally interrupted by reward history, this remitted over time in the young adult participants, whereas the intrusive effects of reward history persisted in adolescents. Age-related changes in functional connectivity between rIFG–vmPFC paralleled the age-dependent effects of reward history on inhibitory control. Taken together, these findings suggest that age-related maturation in prefrontal connectivity may be associated with the differential integration of learned value with inhibitory control with age.

This study employed a two-part task in which, first, an initially neutral stimulus acquired an association between approaching and receiving a monetary reward, and a second neutral stimulus was experienced with equal frequency but was not associated with rewarding outcomes. RT speeding and subjective reports demonstrated that the acquisition of the reward conditioned response did not vary by age. Some previous work has also shown age invariance in general value learning between adolescents and adults in humans (Hauser, Iannaccone, Walitza, Brandeis, & Brem, 2015; van den Bos, Güroğlu, van den Bulk, Rombouts, & Crone, 2009; Galvan et al., 2006) and rodents (Meyer & Bucci, 2016; Simon, Gregory, Wood, & Moghaddam, 2013; Sturman, Mandell, & Moghaddam, 2010). However, mechanisms supporting equivalent seeming value learning can differ over development (see Davidow, Insel, & Somerville, 2018, for a review), and there are circumstances that results in worse learning (e.g., Palminteri, Kilford, Coricelli, & Blakemore, 2016) or better learning (e.g., Davidow, Foerde, Galván, & Shohamy, 2016) in adolescents compared with adults. More research is needed to draw general inferences about the factors that influence the development of value learning.

The second phase of the task consisted of an inhibitory control task with two no-go targets—the previously rewarded and previously unrewarded cues. The intrusion on inhibitory control from reward history exerted a negative influence beginning in adolescence and intensifying with increasing age, which is broadly consistent with previous research into reward-related processes showing a shift in approach behavior toward appetitive cues between childhood and adolescence (Somerville et al., 2011; Galvan et al., 2006). However, unlike some studies of adolescent reward-related approach behaviors, we did not observe a nonlinear, adolescent-peaking effect. These prior studies have shown a greater disruption in adolescents' cognitive control by stimuli with "active" reward qualities (i.e., immediately rewarding or the cue itself holds intrinsic reward), whereas this study suggests that adolescents' cognitive control may be less disrupted when reward value is symbolic or temporally distal. Altlhough additional work is needed, these findings suggest that abstract reward association is not sufficient to uniquely disrupt adolescents' inhibitory control. Moreover, these findings could not be explained by differential motor invigoration induced by the reward association, strengthening the inference that the reward history modulated inhibitory control processes.

The interaction between reward history and age was additionally qualified nonlinearly by time within the task. In this study, early in the task, the youngest participants showed a nominal benefit for inhibitory control from reward history. This is consistent with previous work in children (ages 3–12) where the enduring effect of reward facilitated inhibitory control by increasing the salience of the previously reward cue (Winter & Sheridan, 2014). The disruption of inhibitory control from the reward history persisted across time in late adolescents, whereas it remitted over time in young adults. This is consistent with previous work comparing the enduring effect of reward on attention where adolescents continued to be distracted by a previous reward association longer than adults (Roper et al., 2014). One possibility is that, although the processes that lead to impairment from reward history emerge during adolescence, the processes that allow one to overcome the impairment from reward history develop later (see Davidow et al., 2018, for a commentary). This could result in a more temporally persistent disruptive effect of reward influence for adolescents than for adults. Together, these behavioral findings suggest that one key transition for goal-directed behavior over development is the ability to update a previously held representation to reflect new incoming information about value.

We also observed behavioral improvement in inhibitory control with age irrespective of reward history. This age-related gradual improvement in control is consistent with prior research evaluating inhibitory control for neutral cues (Rubia et al., 2006; Luna et al., 2001; Casey et al., 1997). The general behavioral improvement in overall inhibitory control over development was paralleled by age-related increases in rIFG recruitment in response to correct no-go trials (i.e., when inhibitory control was achieved). Across all participants independent of age, we observed greater recruitment of rIFG when successfully withholding a response to the previously rewarded compared with the previously unrewarded no-go target. One interpretation of this finding is that the history of reward increased inhibitory control demands over and above those elicited by the previously unrewarded stimulus. Moreover, as reward history disruption to inhibitory control behaviorally intensified with age, we observed a parallel shift in functional coupling between the rIFG and vmPFC. This suggests that changing functional coordination among prefrontal regions with age facilitates the selection of goal-directed actions over valued stimuli.

A limitation of this study is that it was not designed to test for changes in task-based functional connectivity over time. Future research is needed to probe the temporal dynamics of this age-related connectivity shift along with changes in the degree of behavioral disruption by reward history.

Though IFG–vmPFC functional connectivity development has not been a focus in prior work on inhibitory control and value interactions, there are parallels with conceptually related work in adults on goal-directed decisions and action selection. Prior work in adults has implicated IFG–vmPFC coupling in support of healthier food choices in dieters (Hare, Camerer, & Rangel, 2009), which is thought to be a form of effortful control. Investigations of control for food craving over development have shown increased activation in IFG with increasing age when resisting cravings and vmPFC activation to desirable foods that does not differ with age (Giuliani & Pfeifer, 2015; Silvers et al., 2014) but did not examine connectivity among these regions. Though desirable foods may be inherently rewarding, in a goal state of dieting, such reward associations need to be regulated. Thus, this goal state shares features with this study where a cue that was rewarding no longer confers reward at the time control is required. Together with previous work, the change in functional coupling with increasing age observed in this study may reflect goal-related control over once-valued cues.

Generally, the present task forms an instrumental reward association and measures the degree and durability of inhibitory control disruption as a function of previous learning. What might drive developmental differences in the durability of learned reward? One possibility is that the increase in inhibitory control disruption from previous reward could reflect a persistence in maintaining a learned reward–cue association via developmental differences in extinction processes (Waters, Theresiana, Neumann, & Craske, 2017; Meyer & Bucci, 2016; Sturman et al., 2010), as the previously associated reward outcome no longer occurs during the inhibitory control task. Extinction of learning cannot be directly measured in this study because the behavioral index of learning that was measured during conditioning (i.e., button press) is no longer being measured for the same cues in the novel context (i.e., measuring withholding button press). If extinguishing previous learning is underlying inhibitory control improvements, it is possible that these processes contribute to the persistence of the previous reward disruption in older adolescents compared with young adults. Consistent with this result, juvenile rodents extinguished less for a cue that had been conditioned with continuous reinforcement, whereas adult rodents did not exhibit this perseveration (Meyer & Bucci, 2016). Juvenile and adult rodents had showed no differences in learning during conditioning (Meyer & Bucci, 2016), consistent with the lack of age differences during conditioning in this study. However, unlike in extinction, the new value contingency during the inhibitory control task is explicitly instructed and thus does not require new learning from experience. Future research is needed to examine the role of extinction or new learning on value associations and the enduring influence of previous reward learning on later inhibitory control.

Alternatively, the age-related differences observed in this study could be related to attentional differences at different ages. Previous work in adults has demonstrated that a learned reward association drives involuntary attention, described as "value-driven attentional capture" (Anderson, Laurent, & Yantis, 2011). This enhanced attention to the previously rewarded no-go stimulus may be a source of the intrusion into task goals. In a similar paradigm implemented in 13–16 year olds, increased attentional capture from a reward history led to longer lasting intrusive effects from the previous reward in adolescents when compared with adults (Roper et al., 2014). If the greater activation in the rIFG observed for the previously rewarded target reflects heightened salience of the value-associated target, then the age-dependent functional coupling observed between the rIFG and vmPFC could reflect greater value-driven attention with increasing age. Future work on the development of reward effects on goal-directed behavior will need to distinguish between inhibitory control and the influence of attention on control and the underlying maturing prefrontal circuitry interactions that support these processes.

Conclusion

Developmental improvements in inhibitory control are an important aspect of emerging goal-directed behavior. We have shown that the transition from late childhood to early adulthood is associated with greater susceptibility to challenges of inhibitory control from learned reward associations. This is paralleled by ongoing development of connectivity among networks in the brain known to be important for supporting abstract representation of both goals and value in adults. These findings add to the growing literature demonstrating the complex and dynamic shifts in goal-directed behavior with development, revealing that learned reward disrupts inhibitory control most persistently in the transition from adolescence into adulthood. This distinction helps unravel the particular contexts in which adolescents and adults are differentially equipped to exert goal-directed behavior in the face of competing environmental demands.

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