

Immaturities in Reward Processing and Its Influence on Inhibitory Control in Adolescence

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The nature of immature reward processing and the influence of rewards on basic elements of cognitive control during adolescence are currently not well understood. Here, during functional magnetic resonance imaging, healthy adolescents and adults performed a modified antisaccade task in which trial-by-trial reward contingencies were manipulated. The use of a novel fast, event-related design enabled developmental differences in brain function underlying temporally distinct stages of reward processing and response inhibition to be assessed. Reward trials compared with neutral trials resulted in faster correct inhibitory responses across ages and in fewer inhibitory errors in adolescents. During reward trials, the blood oxygen level-dependent signal was attenuated in the ventral striatum in adolescents during cue assessment, then overactive during response preparation, suggesting limitations during adolescence in reward assessment and heightened reactivity in anticipation of reward compared with adults. Importantly, heightened activity in the frontal cortex along the precentral sulcus was also observed in adolescents during reward-trial response preparation, suggesting reward modulation of oculomotor control regions supporting correct inhibitory responding. Collectively, this work characterizes specific immaturities in adolescent brain systems that support reward processing and describes the influence of reward on inhibitory control. In sum, our findings suggest mechanisms that may underlie adolescents' vulnerability to poor decision-making and risk-taking behavior.

Keywords: adolescence, antisaccade, fMRI, response inhibition, reward

Introduction

Negative outcomes associated with risky or reckless behaviors are a major contributor to sharp increases (~200%) in morbidity and mortality rates observed during adolescence (Arnett 1992; Spear 2000; Dahl 2004). Risk taking can be defined as engaging, often impulsively, in behaviors that are high in subjective desirability or excitement but which expose the individual to potential injury or loss (e.g., driving extremely fast and engaging in unprotected sex) (Irwin 1990). Adolescents' propensity to engage in risk taking provides compelling behavioral evidence for immaturities in decision-making abilities. However, our understanding of the neural basis of risk taking remains limited. Although multiple functional circuitries are expected to contribute to behavioral risk taking, 2 likely primary systems are reward processing and inhibitory control (Steinberg 2004). Immature detection and appraisal of rewards coupled with limitations in endogenous impulse control could result in poor decision making that may then set the stage for engaging in risk taking. In order to inform the neural basis of risk-taking behavior, in this paper, we compare

reward processing and its effects on inhibitory control in adolescents compared with adults.

An extensive literature has delineated the neural circuitry supporting reward processing in mature adults (Schultz 2000; Breiter et al. 2001; O'Doherty et al. 2001; Roesch and Olson 2004; Hikosaka et al. 2006). In particular, the orbitofrontal cortex (OFC), dorsal and ventral striatum (VS), and medial prefrontal cortex (PFC) have been identified as key components (Schultz 2000; McClure et al. 2004). Importantly, the temporal resolution of single-unit and event-related functional magnetic resonance imaging (fMRI) studies has shown that reward processing is not a monolithic function but rather a dynamic suite of interrelated computations. Distinct signals occurring before ("anticipatory" signals) and after reward delivery ("consummatory" signals) have been identified (Schultz 2000; Hare et al. 2008). Anticipatory signals are associated with the initial detection and determination of the valence of reward-predicting cues, as well as with assessment of the anticipated value of a future reward (Knutson et al. 2001; O'Doherty et al. 2002). Consummatory signals include those related to the magnitude of the received reward (Delgado et al. 2000, 2003; Rolls 2000; O'Doherty et al. 2001) and whether or not the received reward matched up with predictions ("prediction-error" signals) (Schultz 2000; Schultz et al. 2000).

Comparatively, our understanding of the development of reward processing through adolescence remains quite limited. Anatomical studies indicate that primary reward regions show persistent immaturities through adolescence, including continued thinning of gray matter in basal ganglia and OFC (Giedd et al. 1996; Sowell et al. 1999; Gogtay et al. 2004; Toga et al. 2006), which in part are likely due to the loss of weak or unused synapses via synaptic pruning (Gogtay et al. 2004). During adolescence, an increased number of underspecified synapses could result in limitations in the identification of reward cues and value representations relative to adults. In parallel with synaptic pruning, myelination increases linearly throughout development (Yakovlev and Lecours 1967). Myelination enhances the efficiency of information processing by increasing the speed and fidelity of distal neuronal transmission, aiding the functional integration of the widely distributed brain circuitry critical for the emergence of complex higher-order behavior (Goldman-Rakic et al. 1992; Luna and Sweeney 2004). A comparative undermyelination of the adolescent brain could contribute to a limited ability to efficiently integrate reward signals with efferent motor systems necessary for motivated behavior (Roesch and Olson 2003, 2004).

Along with persistent microstructural maturation, converging data from human and animal models indicate that dopamine (DA) neurotransmission in striatal and cortical systems

continues to mature during adolescence (Spear 2000; Andersen 2003; Crews et al. 2007). For example, D1- and D2-receptor levels and binding in rat striatum are greater during adolescence compared with adulthood (Seeman et al. 1987). The density of DA transporters, which function to remove DA from the synapse, peaks during adolescence in the striatum (Meng et al. 1999). Moreover, DA inputs to PFC increase in adolescence (Kalsbeek et al. 1988; Rosenberg and Lewis 1994, 1995; Spear 2000), and evidence suggests a relative shift from mesolimbic to mesocortical DA systems during early adolescence (Spear 2000). In terms of reward processing, increases in adolescent DA levels in striatum and PFC coupled with greater DA transporters could contribute to a heightened but temporally limited sensitivity to rewards, as proposed in a model of attention deficit hyperactivity disorder (Castellanos and Tannock 2002).

In accord with structural data, initial developmental fMRI studies indicate functional immaturities in reward-related brain systems during adolescence (Bjork et al. 2004, 2007; May et al. 2004; Ernst et al. 2005; Galvan et al. 2006; Guyer et al. 2006; van Leijenhorst et al. 2006, 2009; Eshel et al. 2007). Although adolescents have been shown to recruit a reward circuitry that is similar to adults (May et al. 2004), the directionality of immature responses has not yet been fully characterized in primary regions. Evidence has been found for adolescent “under” activity during anticipatory processing in the VS as well as during probabilistic decision making in OFC and mesial PFC (Bjork et al. 2004, 2007; Eshel et al. 2007), but “over” activity in VS during reward receipt (consummatory) processing (Ernst et al. 2005; Galvan et al. 2006). Thus, different temporal phases of reward processing (anticipatory vs. consummatory) may have distinct developmental trajectories, an important consideration for theoretical models that broadly characterize the adolescent reward system as either hyperactive (Chambers et al. 2003; Ernst et al. 2006) or hypoactive (Spear 2000), relative to adults.

In parallel with the on-going maturation of reward processing, refinements in inhibitory control also continue through adolescence (Paus et al. 1990; Levin et al. 1991; Ridderinkhof et al. 1999; Ridderinkhof and van der Molen 1997; Williams et al. 1999; Bunge et al. 2002; Luna et al. 2004; Liston et al. 2006). Voluntary response inhibition refers to the cognitive ability to halt a prepotent response in favor of goal-appropriate action and is a basic component of decision making (Curtis and D’Esposito 2003; Luna et al. 2004; Ridderinkhof, van den Wildenberg, et al. 2004; Curtis and D’Esposito 2008). Behavioral work from our laboratory and others using the antisaccade (AS) task (Hallett 1978), in which subjects must inhibit the strong urge to saccade toward a suddenly appearing peripheral target and instead look toward the mirror location, indicates that adult-like levels of response inhibition begin to stabilize in mid- to late adolescence (Fischer et al. 1997; Munoz et al. 1998; Klein and Foerster 2001; Luna et al. 2004). However, the neural circuitry supporting AS task performance shows continued immaturities through adolescence, including reduced activation in frontal eye field (FEF) and an increased reliance on lateral prefrontal systems relative to adults (Luna et al. 2001, 2004; Velanova et al. 2008). These data support a number of other studies that indicate that the development of circuits which support inhibitory control is protracted (Casey et al. 1997; Rubia et al. 2000; Luna et al. 2001; Adleman et al. 2002; Bunge et al. 2002; Tamm et al. 2002; Durston et al. 2006; Marsh et al. 2006; Rubia et al. 2006, 2007; Velanova et al. 2008).

A more complete understanding of the limitations evident in adolescent decision-making and risk-taking behaviors may be achieved by characterizing the maturation of reward processing along with the influence of rewards on inhibitory control. To date, only a handful of behavioral studies have investigated the interaction of these systems using modified AS tasks with trial-by-trial monetary reward contingencies (Duka and Lupp 1997; Blaukopf and DiGirolamo 2006; Jazbec et al. 2006; Hardin et al. 2007). On the one hand, adding a reward contingency has been shown to reduce the number of inhibitory errors generated by adolescents and adults, suggesting that basic pathways between reward-related regions and oculomotor control-related regions are established at least by adolescence. On the other hand, rewards differentially affect other saccade metrics (e.g., velocity and latency) across development (Jazbec et al. 2006; Hardin et al. 2007). However, the developmental differences in the neural circuitry supporting performance of the rewarded AS task has not yet been characterized in the literature.

We aimed to characterize developmental differences in reward processing and effects of reward on response inhibition in healthy adolescents and adults. We note that examining the interaction between these 2 model systems should be considered an initial step toward characterizing the more complex phenomenon of risk taking. Critically, we use a novel set of methods including a monetary incentive-mediated AS paradigm presented in a fast, event-related fMRI design with partial “catch” trials (Ollinger, Shulman, and Corbetta 2001) that allows us to dissociate and separately characterize blood oxygen level-dependent (BOLD) activity associated with reward processing components previously identified in the literature to be distinct (Schultz 2000). These components include reward cue identification (Schultz 2000), anticipating responding for a reward (Bjork et al. 2004), and response/feedback (Ernst et al. 2006), each of which could have different developmental trajectories. This approach is particularly unique in that we examine 2 components of anticipatory processing—initial cue assessment and later response preparation/anticipation. Moreover, we aimed to simultaneously characterize the effects of reward contingencies on distributed oculomotor control regions (e.g., putative cortical eye fields) known to be critical to AS task performance (Munoz and Everling 2004).

In line with previous behavioral reports, we predicted that adults and adolescents would generate fewer inhibitory errors on reward compared with neutral AS trials (Jazbec et al. 2006; Hardin et al. 2007). During reward versus neutral trials, we hypothesized that both age groups would show increased activity in brain regions supporting reward-cue detection (e.g., VS) and value representations (e.g., VS and OFC). Further, we hypothesized that correct AS performance on rewarded trials would be supported by increased activity in oculomotor control circuitry, specifically areas near the superior precentral sulcus (SPS; putative human homolog of FEF), which is known to support correct AS performance. Enhanced activity in FEF fixation neurons during the preparatory period of AS trials has been shown to be crucial to the ability to inhibit erroneous responses (Connolly et al. 2002; Curtis and D’Esposito 2003; Munoz and Everling 2004). Given evidence for suboptimal AS performance and immaturities in reward processing in adolescence, we hypothesized that adolescents would show a more pronounced effect of reward modulation of oculomotor regions and behavioral performance. Finally, based on previous findings, we also hypothesized that adolescents would show

hypoactivity during reward anticipation (Bjork et al. 2004, 2007; Eshel et al. 2007) and hyperactivity during consummatory processing (Ernst et al. 2005; Galvan et al. 2006).

Materials and Methods

Participants

Thirty-eight healthy subjects (22 adolescents and 16 adults) were initially recruited for this study. Imaging data from 4 adolescents were excluded from analyses due to excessive head motion in the scanner. The remaining 34 subjects (18 adolescents [aged 13–17 years, $M = 15.3$ (± 1.5), 8 females], and 16 young adults [aged 18–30 years, $M = 21.7$ (± 2.9), 10 females]) met the following inclusion criteria: All had far visual acuity of at least 20/40 (corrected or uncorrected) and medical histories that revealed no neurological disease, brain injury, or major psychiatric illness in the subject or first degree relatives determined by interview. Age ranges for each group were selected based on previous work indicating differential behavioral performance levels on the AS task (Luna et al. 2004; Scherf et al. 2006). Participants and/or their legal guardians provided informed consent or assent prior to participating in this study. Experimental procedures for this study complied with the Code of Ethics of the World Medical Association (1964 Declaration of Helsinki) and the Institutional Review Board at the University of Pittsburgh. Subjects were paid for their participation in the study.

Rewarded AS Task

On each AS trial, subjects were initially presented with one of 2 incentive-indicating cues (1.5 s) (Fig. 1). A ring of green dollar bill signs (\$), each subtending approximately 1° of visual angle, surrounding a central white fixation cross indicated that the subject would win money if they correctly performed the forthcoming trial. An equivalently sized, isoluminant ring of blue pound signs (#) indicated that no money was at stake on that trial. Subjects were not told exactly how much money could be earned on each trial to prevent their keeping a running tally of their performance and engaging working memory systems. However, subjects were told prior to the task that they could win up to an additional \$25 contingent on their

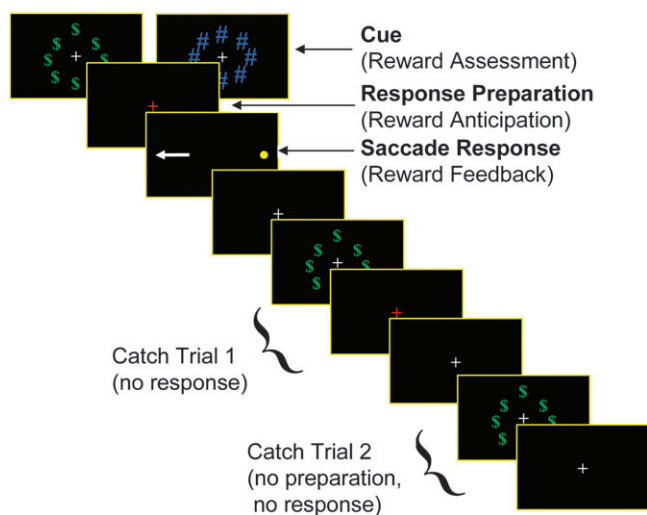


Figure 1. Depiction of the monetary incentive AS task. A ring of green dollar bill signs indicated that the subject could win money if they correctly performed the forthcoming trial (reward condition). A ring of blue pound signs indicated that there was no money at stake (neutral condition), regardless of performance. Each incentive cue was presented for 1.5 s. Following the cue, the fixation cross turned red to indicate the response preparation period (1.5). Finally, a peripheral light appeared for the first 75 ms of a 1.5-s saccade response period. Two variants of catch trials were used and consisted of the trial terminating either after the response preparation (labeled “Catch Trial 1”), or after the incentive cue (labeled “Catch Trial 2”). A white fixation cross was presented (jittered between 1.5, 3, and 4 s) between all trials.

performance and that no debt would be accrued (i.e., subjects could not owe money). Next, the incentive ring disappeared, and the central fixation cross changed from white to red (1.5 s), indicating to the subject that they should begin to prepare to inhibit a response. Finally, a peripheral stimulus (yellow dot) appeared (75 ms) at an unpredictable horizontal location ($\pm 3^\circ$, 6° , and 9° visual angle). Subjects were instructed not to look at the stimulus when it appeared but instead direct their eyes to the mirror location during this time (1475 ms).

To uniquely estimate the hemodynamic response evoked during each trial epoch, our experimental design included approximately 30% partial catch trials, randomly inserted, along with jittered intertrial intervals (Ollinger, Corbetta, and Shulman 2001; Ollinger, Shulman, and Corbetta 2001). The inclusion of these elements assured that there were a sufficient number of independent linear equations to separately estimate the BOLD response associated with the cue, response preparation, and saccade response epochs during deconvolution. This is a quantitatively validated approach to estimating components within a trial (Ollinger, Corbetta, and Shulman 2001; Ollinger, Shulman, and Corbetta 2001; Goghari and MacDonald 2008), and it has been previously reported in the literature (Shulman et al. 1999; Corbetta et al. 2000; Wheeler et al. 2005; Brown et al. 2006). The 30% catch trial rate minimized subjects’ anticipation of a partial trial, while maintaining a sufficient frequency of “whole” trials to allow proper estimation of the BOLD response. Two catch trial variants were presented throughout each run and consisted of the trial terminating after either 1) the response preparation period (red fixation) (i.e., no peripheral cue for the motor response was shown) or 2) the incentive cue images (circles of “\$” or “#”) (i.e., red fixation and peripheral cue were not displayed). It is important to note that subjects did not know which trials would be partial catch trials and which were whole trials until the partial trials terminated because the initial partial trial components (cue, preparatory fixation) were presented exactly as in whole trials. Prior to imaging, subjects were told that some trials would be incomplete and that they should simply continue on with the next trial as indicated. The intertrial fixation period was jittered between intervals of 1.5, 3, or 4.5 s (uniformly distributed) and consisted of subjects simply fixating a central white cross on a black background. In each run, 14 complete reward trials, 6 partial reward catch trials (3 of each variant), 14 complete neutral trials, and 6 partial neutral catch trials (3 of each variant) were presented in random order. Each run was 5 min 9 s in duration. Four runs were presented per experimental session, for a total of 56 complete reward trials and 56 complete neutral trials.

Eye Tracking

Subjects were first tested in our behavioral laboratory within 1 week prior to scanning to confirm that they understood and were able to perform the task as described. In the MR scanning environment, eye movements were obtained with a long-range optics eye-tracking system (Model 504LRO; Applied Science Laboratories, Bedford, MA) that recorded eye position by pupil-corneal reflection obtained by a mirror mounted on the head coil with a resolution of 0.5° of visual angle. Simultaneous video monitoring was also used to assure task compliance. At the beginning of the experimental session and between runs when necessary, a 9-point calibration procedure was performed. Stimuli were presented using E-Prime (Psychology Software Tools, Inc., Pittsburgh, PA), projected onto a flat screen positioned behind the magnet. Subjects viewed the screen using a mirror mounted on a standard radiofrequency head coil. Eye data were scored off-line using ILAB software (Gitelman 2002) and an in-house scoring suite written in MATLAB (MathWorks, Inc.) running on a Dell Dimension 8300 PC. Variables of interest included correct and incorrect AS latencies and correct AS response rate (1 minus the number of inhibitory failures/total number of scorable trials) on rewarded and neutral trials. A correct response in the AS task was one in which the first eye movement during the saccade response epoch with velocity greater than or equal to $30^\circ/s$ (Gitelman 2002) was made toward the mirror location of the peripheral cue and extended beyond a 2.5° visual angle central fixation zone. Eye movements on partial catch trials were rare given that subjects were never cued to a specific location and not scored. AS errors (also referred to as prosaccade errors) occurred when the first saccade during the saccade response epoch was directed

toward the suddenly appearing peripheral stimulus and exceeded the 2.5°/visual angle central fixation zone. Trials where no eye movements were generated (<1% of trials) were excluded from further analyses.

fMRI Acquisition and Preprocessing

Imaging data were collected using a 3.0-T Siemens Allegra scanner at the Brain Imaging Research Center, University of Pittsburgh, Pittsburgh, PA. A gradient-echo echo-planar imaging sequence sensitive to BOLD contrast (T_2^*) was performed (Kwong et al. 1992; Ogawa et al. 1992). The acquisition parameters were time repetition, TR = 1.5 s; time echo = 25 ms; flip angle = 70°; single shot; full k -space; 64×64 acquisition matrix with field of view = 20×20 cm. Twenty-nine 4-mm-thick axial slices with no gap were collected, aligned to the anterior and posterior commissure (AC-PC line), generating $3.125 \times 3.125 \times 4$ mm voxels, which covered the entire cortex and most of the cerebellum. A 3D volume magnetization prepared rapid acquisition gradient-echo (MP-RAGE) pulse sequence with 192 slices (1-mm slice thickness) was used to acquire structural images in the sagittal plane.

Functional images were first preprocessed using FMRIB software library (Smith et al. 2004). Slice-timing correction was performed to adjust for interleaved slice acquisition. Rotational and translational head motion estimates were calculated, and images were corrected by aligning each volume in the time series to the volume obtained in the middle of the acquisition. For each subject, translational and rotational movements were averaged across images and used to calculate total root mean square movement measures. Subjects who moved more than 1 mm (translational) or 1° (rotational) were excluded from subsequent analyses. Four adolescents were excluded based on these criteria.

Structural images (MP-RAGE) were affine registered to functional images and transformed to the same dimensions using the FLIRT utility available in FSL (Jenkinson and Smith 2001). Brain extraction was performed using the brain extraction tool in FSL (Smith 2002). Functional images were spatially smoothed with a 5-mm full-width at half maximum kernel and subjected to high-pass temporal filtering ($\sigma = 37.5$ s) to remove low-frequency scanner drift. Finally, signal intensity for each run was scaled to a mean of 100, and multiple runs were concatenated.

Analysis of functional neuro-images (Cox 1996) was used for individual subject deconvolution as well as group statistical analyses. Deconvolution methods followed steps delineated in Ward (2002). Briefly, our model consisted of 6 orthogonal regressors of interest (reward cue, neutral cue, reward preparation, neutral preparation, reward saccade response, neutral saccade response; “correct AS trials only”). We also included regressors for reward and neutral error trials (consisting of the entire trial), regressors for baseline, linear, and nonlinear trends, as well as 6 motion parameters included as “nuisance” regressors. A unique estimated impulse response function (IRF, i.e., hemodynamic response function) for each regressor of interest (reward and neutral cue, preparation, and saccade; “correct AS trials only”) was determined by a weighted linear sum of 5 sine basis functions multiplied by a data determined least squares-estimated beta weight. The estimated IRF reflects the estimated BOLD response to a type of stimulus (e.g., the reward cue) after controlling for variations in the BOLD signal due to other regressors. We specified the duration of the estimated response from stimulus onset (time = 0) to 18-s poststimulus onset (13 TR), a sufficient duration for the estimated BOLD response to return to baseline, for each separate epoch of the trial. We made no assumptions about its specific shape beyond using zero as the start point. Several goodness-of-fit statistics were calculated including partial F-statistics for each regressor and t -scores comparing each of the 5 estimated beta weights with zero. Following deconvolution, statistical images were transformed into Talairach space (Talairach and Tournoux 1988).

Group-Level Analyses

Anatomical Regions of Interest (ROIs)

Our analyses focused on functionally defined clusters identified within the boundaries of several a priori anatomical ROIs (Curtis and Connolly 2008) previously identified as serving in various aspects of reward processing or oculomotor control. Putative reward-related anatomical ROI in this study included the VS (including nucleus accumbens), OFC,

and ventral medial PFC (VMPFC). We defined the boundaries of the anatomical reward-related ROI used in this study as follows: The VS (Breiter et al. 1997; Breiter and Rosen 1999; Bjork et al. 2004; Voorn et al. 2004) was considered to be bounded dorsally by a line extending laterally from the ventral tip of the lateral ventricle to the internal capsule, the lateral and anterior boundary was the ventral-medial junction of the caudate and putamen, and the posterior boundary was considered to be the anterior commissure. The OFC encompassed the orbital gyrus and rectus gyrus, including BA 10, 11, and 47 (Kringelbach and Rolls 2004). Laterally, the OFC was bounded by the inferior frontal sulcus and on the medial surface by the superior rostral sulcus. The VMPFC referred to the cortex dorsal to the superior rostral sulcus on the medial surface of the brain, anterior and ventral (subcallosal area) to the genu of the corpus callosum, primarily including posterior/medial BA 10 and 32 (Knutson et al. 2003; Blair et al. 2006). The VMPFC included the rostral anterior cingulate cortex.

Putative oculomotor control ROI included areas along the superior and inferior precentral sulcus (sPCS and iPCS, respectively) and paracentral sulcus (paraCS), as well as cingulate cortex (BA 24, 32), including dorsal and caudal anterior cingulate, intraparietal sulcus (IPS), putamen, and dorsolateral PFC (DLPFC, including BA 9, 46) (Sweeney et al. 1996; Grosbras et al. 1999; Liddle et al. 2001; Luna et al. 2001; Connolly et al. 2002; Munoz and Everling 2004; Ridderinkhof, Ullsperger, et al. 2004; Pierrot-Deseilligny et al. 2005; Brown et al. 2006; Hikosaka et al. 2006; Curtis and Connolly 2008). The human precentral sulcus often consists of 2 parts, the superior and inferior precentral sulci, separated by a transverse connection between the precentral and intermediate frontal gyri (Ono et al. 1990). The paraCS was defined as the sulcus anterior to the central lobule along the dorsal medial surface of the brain (Ono et al. 1990). The IPS was defined as the sulcus dividing the superior and inferior parietal lobules (IPL).

Finally, although it has been well established in the literature that across different vascular territories, there are no differences in the hemodynamic response (HDR) function from childhood through adulthood (Kang et al. 2003; Wenger et al. 2004; Brown et al. 2005), we included visual cortex (BA 17, 18) as an additional control region to further demonstrate that adolescents generate time courses that are equivalent to adults.

Time Course Analyses

Estimated IRF values obtained from each subject's deconvolution analysis were entered into an omnibus voxelwise analysis of variance (ANOVA) with time (0 through 12 TR), incentive type (reward, neutral), and age group (adolescent, adult) as fixed factors and subjects as the random factor. Deconvolution methods for our task design, where different stages of a trial are identified, generate estimated IRFs. The IRF reflects the estimated BOLD response to a type of stimulus (e.g., the reward cue) after controlling for variations in the BOLD signal due to other regressors. The mean IRF (also referred to as the mean estimated time course, below) plots show the average (across subjects) estimated BOLD response from the onset of the stimulus (time = 0) to 18-s poststimulus onset. The 18-s duration, a parameter that we specified in our deconvolution model, is an appropriate duration for a typical hemodynamic response evoked by a short duration stimulus to return to baseline.

Separate ANOVAs were run for each trial epoch, resulting in “cue,” “response preparation,” and “saccade response” group images (main effect of time images). The “main effect of time” image shows regions that are significantly modulated across time (0–12 TR) relative to baseline collapsed across subjects and conditions, therefore delineating the basic circuitry recruited in our study. Statistical maps (Fig. 3) were overlaid on the anatomical image from a representative subject. For 3D cortical surface images (Figs. 4–6), we projected foci from regions showing age- and/or incentive-related effects onto the surface of the Human PALS atlas using Caret software (version 5.51) (Van Essen et al. 2001; Van Essen 2002).

Within each “main effect of time” image, functionally defined ROIs (also referred to as “clusters,” below) were next identified using methods already established in the literature (Wheeler et al. 2005; Velanova et al. 2008). First, peak voxels that exceeded a threshold of $P < 0.001$ (uncorrected) were identified and sorted by magnitude of the F-statistic. Next, a 9-mm diameter sphere mask was centered on each maximum. We then corrected the main effect of the time image for multiple comparisons using criteria from a Monte Carlo simulation

(<http://afni.nimh.nih.gov/afni/doc/manual/AlphaSim>), which indicated that a cluster size of at least 17 contiguous voxels was required along with an individual voxel P value of 0.001 in order to achieve a corrected image-level significance of $P < 0.05$. Functional ROIs were defined by including all the voxels that fell within the 9-mm sphere centered on maximum in the uncorrected image and then excluding voxels that failed to pass corrections for multiple comparisons. We then used these functionally defined clusters as masks and extracted the estimated time courses from the constituent voxels for each subject and across both incentive conditions. In this manner, we ensured that the same regions were being considered across subjects. Time courses were averaged across subjects and then analyzed with repeated measures ANOVA; age group (adult, adolescent) served as the between subjects factor; time (0–12 TR) and incentive condition (reward, neutral) were within subjects factors. Unless otherwise noted, sphericity corrected (Greenhouse-Geisser) levels of significance are reported. Below, we report all regions identified in the omnibus “main effect of time” group map, and we provide figures for time courses for regions demonstrating significant age by time, incentive by time, and/or age by incentive by time interactions across the entire estimated response (13 time points).

We note that in several regions examined, the mean estimated time course response demonstrated a biphasic response or a temporally later peak (occurring more than 6 s after the onset of the trial component). It is currently unclear whether the temporally later peaks have functional significance (e.g., reflecting individual subject variability in the recruitment of a specific region or delayed signaling in a region) or are simply a result of our deconvolution analyses that do not assume a fixed HDR shape. As such, we also conducted a secondary, more conservative repeated measure ANOVA that only considered the estimated responses at TRs 3–6. These time points were chosen as they encompass 3–7.5 s after stimulus onset, which would capture the initial peak in a stereotyped hemodynamic response, which would occur between 4 and 6 s after stimulus presentation. Time courses from all ROIs identified in the omnibus main effects of time map for each trial epoch were also analyzed using this approach. For each of these analyses, only “correct” AS trials were analyzed. Finally, we note that the feasibility of comparing BOLD time courses across developmental age groups in a common stereotaxic space has been well established (Kang et al. 2003; Wenger et al. 2004; Brown et al. 2005).

As a validity check for our deconvolved time courses from the separate trial epochs, we sought to verify that the sum of the individual trial components would result in a typical HDR shape and that the summed response closely matched the time course obtained when considering the trial as a whole. To do so, we first summed the estimated time courses from each individual trial epoch (cue + response preparation + saccade response) in each voxel of the brain, shifting the response preparation epoch time course by 1.5 s to account for the onset of this component in a trial and the saccade response epoch time course by 3 s. Next, the IRF for the whole trial (i.e., cue, preparation, and response together) in each voxel was generated by running a separate deconvolution analysis in which we coded only the start of each trial and estimated the response up to 21 s after the trial onset. Each of these time courses (cue, response preparation [time shifted], saccade response [time shifted], summed response, and whole-trial response) was then averaged across each voxel identified in the cue “main effect of time” sphere mask and plotted (Supplementary Figs. 1–6). This procedure was then replicated for the response preparation and saccade response sphere masks. This validity check showed that a sum of the component time courses resulted in a typical hemodynamic response, providing additional support that our deconvolution procedures were accurate. Supplementary Figures 1–6 show example plots from our time course-verification analysis. A high degree of similarity was found between summed (thick black lines) and whole-trial (red lines) time courses and canonical HDR profiles.

Results

Behavior

Repeated measures ANOVA on correct inhibitory response rates across age groups and incentive conditions showed

a significant main effect of incentive type ($F(1,32) = 18.9424$, $P < 0.001$) and a trend for a main effect of age group ($F(1,32) = 3.491$, $P = 0.071$) but no age-group by incentive-type interaction. As expected, all subjects consistently followed prosaccade errors with corrective responses to the appropriate location, similar to previous reports (Velanova et al. 2008), indicating that the task instructions were understood, but there had been a failure to inhibit the reflexive saccade.

Given our hypotheses that adults and adolescents would generate fewer inhibitory errors on reward compared with neutral trials, planned comparisons of the effect of incentive type on performance (correct response rate and latency) within each age group (reward vs. neutral for adolescents; reward vs. neutral for adults) were also conducted using Bonferroni adjusted alpha levels of 0.025 per test (0.05/2). Adolescents generated a significantly greater number of correct ASs on rewarded compared with neutral trials ($t(17) = 4.500$, $P < 0.001$) (see Fig. 2A). Adults’ performance showed a trend for improved responses on reward compared with neutral trials ($t(15) = 1.939$, $P = 0.072$).

The latency to initiate a correct AS showed a main effect of incentive ($F(1,32) = 22.695$, $P < 0.001$) but no main effect of age group or age group by incentive interaction. Planned comparisons revealed that both age groups generated significantly faster ASs on reward compared with neutral trials (adolescents, $t(17) = 3.215$, $P = 0.005$ and adults, $t(15) = 3.498$, $P = 0.003$).

The latencies of erroneous saccades (referred to as “prosaccade errors,” when subjects initially look toward the peripheral stimulus) did not show a significant age-group by incentive interaction. Planned comparisons showed that adolescents, but not adults, generated significantly faster responses on rewarded compared with neutral trials ($t(17) = 2.400$, $P = 0.022$). Figure 2B,C plots the latencies of correct and incorrect ASs, respectively. Means and standard deviations for correct response rate and latencies for correct trials are provided in Table 1.

Finally, given the relatively wide age range of adolescents tested, separate within-group comparisons of “older” and “younger” adolescents were conducted to examine the possibility that the age difference between the older adolescents and adults was not large enough to demonstrate differences. That is, if it was the case that older adolescents perform significantly different than younger subjects, then data from the older adolescents could be driving the nonsignificant effects of age. We used a median split to divide the 18 adolescent subjects into older ($N = 9$; 6 17-year-olds and 3 16-year-olds) and younger groups ($N = 9$; 3 13-year-olds, 1 14-year-old, 4 15-year-olds, and 1 16-year-old [the youngest of the 4 16-year-olds tested]). Independent sample t -tests were run on “young” and “old” adolescent correct response rate and latency data for both trial types. No significant differences (all P 's > 0.05) were observed.

fMRI

A distributed network of brain regions was engaged during each trial epoch in both adults and adolescents, including expected oculomotor control regions (e.g., cortical eye fields and basal ganglia) and reward-related regions (e.g., OFC and VS) (Fig. 3). In several loci, we identified significant age and/or incentive interactions with time across either the entire estimated response (13 time points) or TRs 3–6 (see Materials

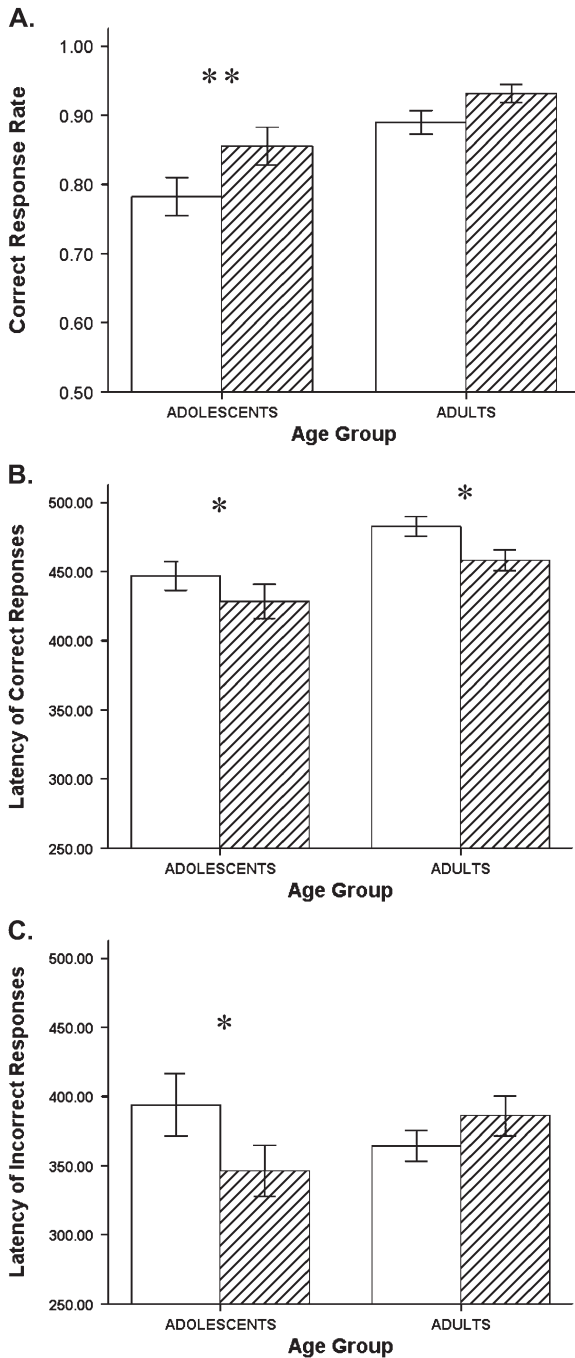


Figure 2. Behavioral results. (A) Correct response rate for adolescents (left bars) and adults (right bars) for neutral (unfilled bars) and rewarded (hashed bars) trials. (B) Latencies of correct ASs. (C) Latencies of inhibitory errors. Single asterisk (*) indicates significance at the 0.05 alpha level; double asterisks (**) indicate significance at the 0.001 alpha level.

and Methods). These results, separated by trial epoch, are discussed in more detail below.

Control Region: Primary Visual Cortex

Functionally defined clusters located in visual cortex (BA 17, 18) during each trial epoch confirmed that adolescents generate a similar HDR compared with adults. The foci examined demonstrated robust participation in the AS task but no interactions of age or incentive type by time (Supplementary Fig. 7).

Epoch 1: Incentive Cue

Reward-Related Regions

During the presentation of the incentive cue, the right VS (Talairach coordinates: 14, 2, -7) showed a significant age by time interaction ($F(12,384) = 3.082, P = 0.023$) when considering the entire estimated time course (13 time points). Adults showed more positive activity during rewards, whereas adolescents showed a negative response. In this region, adolescent reward and neutral time courses showed early negative-going deflections, whereas adults showed a minimal response for rewards followed by a more robust positive response across both trial types (Fig. 4). When considering only the initial aspect of the time course (TRs 3-6), this region still showed a trend ($F(3,96) = 2.368, P = 0.076$). However, left VS (-10, 2, -4) showed a significant age by time interaction ($F(3,96) = 3.204, P = 0.027$) across this shorter time span. Within this range, similar to the right VS, adolescents showed early negative responses in the time courses of reward and neutral trials, whereas adults showed no deflections from baseline.

Oculomotor and Inhibitory Control Regions

None of the oculomotor control ROIs examined showed a significant age by time, incentive by time, or age by incentive by time interaction across the 13 estimated time points during the presentation of the incentive cue. Across TRs 3-6, however, we observed an incentive by time interaction along the right sPCS (26, -13, 53) ($F(3,96) = 2.695, P = 0.05$), right inferior frontal gyrus (44, 11, 32) ($F(3,96) = 4.474, P = 0.006$), as well as left precuneus (-28, -64, 41) ($F(3,96) = 2.959, P = 0.036$). In the left IPL (-28, -52, 38) (BA 7, dorsal and medial to the supramarginal gyrus), an age by incentive by time interaction was observed ($F(3,96) = 3.397, P = 0.021$) (Table 2). In each of these regions, the adolescent reward-trial responses were similar to the adult reward and neutral time courses (Fig. 4). However, adolescents showed attenuated responses in these areas during neutral trials.

Table 3 provides the location of peak voxels for all functional clusters observed in a priori anatomical regions demonstrating significant modulation across time during the incentive cue epoch.

Table 1
Behavioral results for reward and neutral AS trials

| Trial | Correct response rate | | Latencies of correct ASs (ms) | | Latencies of AS errors (ms) | |
|---------|-----------------------|---------------|-------------------------------|----------------|-----------------------------|----------------|
| | Adolescents | Adults | Adolescents | Adults | Adolescents | Adults |
| Reward | 83.45 (22.99) | 93.14 (10.26) | 428.39 (97.62) | 458.21 (59.18) | 341.84 (104.05) | 381.52 (51.24) |
| Neutral | 76.55 (23.12) | 88.97 (13.99) | 446.84 (82.62) | 482.59 (56.18) | 383.23 (164.62) | 355.32 (69.70) |

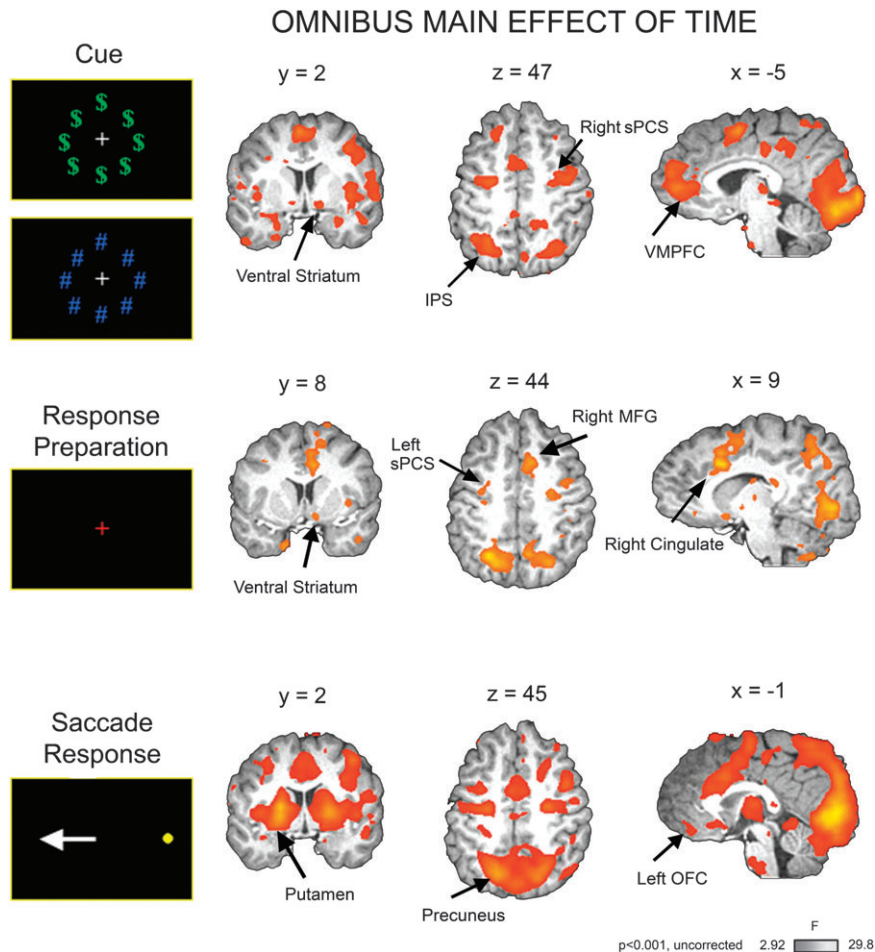


Figure 3. “Main effect of time” group activation maps for incentive cue (ring of dollar signs or pound signs), response preparation (red fixation), and saccade response (peripheral flash), collapsed across incentive type and age group. Image threshold set at $P < 0.001$ (uncorrected). Right side of image = right brain. Abbreviations: sPCS = superior precentral sulcus; IPS = intraparietal sulcus; OFC = orbitofrontal cortex; MFG = medial frontal gyrus; and VMPFC = ventral medial prefrontal cortex.

Epoch 2: Response Preparation/Anticipation

Reward-Related Regions

Following the incentive cue epoch, during response preparation/anticipation, a single cluster in the right VS (11, 8, and -7) showed a significant age by time interaction ($F(12,384) = 2.586$, $P = 0.05$) across the 13 estimated time points. Examination of the time courses from this region revealed a heightened adolescent response during reward compared with neutral trials (Fig. 5). Adults demonstrated little participation of this region with only a weak positive response during neutral trials and a later, negative-going deflection during reward trials in this region. Within the more restricted time range of TRs 3–6, this region still showed a significant age by time interaction ($F(3,96) = 6.618$, $P < 0.001$).

Oculomotor and Inhibitory Control Regions

In the left sPCS (-25, -13, 56), a significant age by incentive by time interaction was observed ($F(12,384) = 2.889$, $P = 0.032$) across the entire estimated trial. In this region, adolescents had a higher early peak relative to adults across both incentive types, as well as a temporally extended response during reward trials (Fig. 5). Considering only TRs 3–6, the age by incentive by time interaction in this region was reduced to a trend ($F(3,96) = 2.282$, $P = 0.084$).

Elsewhere, across TRs 3–6, we observed an age by time interaction in right medial frontal gyrus (MFG)/superior frontal gyrus (17, -10, 53) ($F(3,96) = 2.915$, $P = 0.038$). Significant age by incentive by time interactions were also observed in 2 other clusters along the left sPCS, (-25, -19, 47) ($F(3,96) = 2.920$, $P = 0.038$) and (-31, -10, 44) ($F(3,96) = 2.909$, $P = 0.038$). In each of these regions, adolescent responses during reward and neutral trials were heightened relative to the adults (Fig. 5). More inferiorly, a significant age by incentive by time interaction was observed in the left iPCS (-28, -1, 35) ($F(3,96) = 3.281$, $P = 0.024$). In this region, the adolescent reward response was similar to the adult reward and neutral responses, with each time course peaking at approximately 7.5 s. The adolescent neutral time course reached a smaller magnitude peak earlier (3 s) and fell toward baseline during this time span (Fig. 5). A significant age by incentive by time interaction ($F(3,96) = 3.836$, $P = 0.012$) across TRs 3–6 was also observed in the left MFG/anterior cingulate (-7, 29, 35) (Table 4). Adolescents showed a heightened response to reward relative to neutral trials and to the adult reward and neutral responses.

In the posterior parietal cortex, a cluster in right precuneus (BA 7) (8, -58, 53) showed a significant age by time interaction ($F(12,384) = 3.093$, $P = 0.024$) across the 13 estimated time points. As demonstrated by the time courses from this region

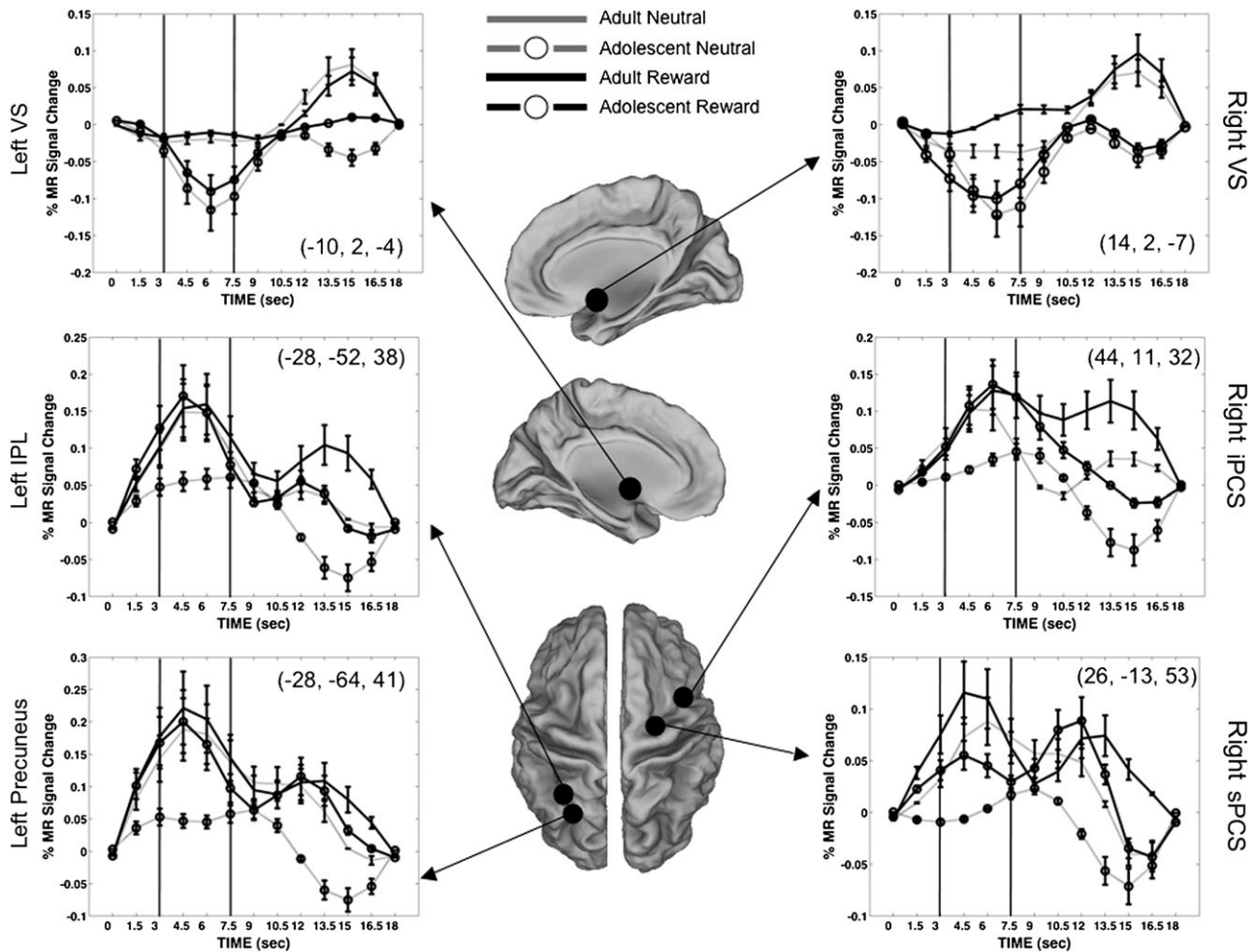


Figure 4. Cue epoch time courses showing age and/or incentive interactions across time. Time courses were extracted from a sphere mask (9-mm diameter) centered on coordinates of peak voxel (see Materials and Methods). For visualization purposes only, filled black circles indicating the location of masks are schematically shown above the surface of the Human PALS atlas, drawn using Caret (version 5.5). (Note that the black circles shown here do not reflect the actual shape of mask.) As indicated in legend, solid black line = adult response during reward trials; solid gray line = adult response during neutral trials; solid black line with circular markers = adolescent response to reward trials; solid gray line with circular markers = adolescent response to neutral trials. Error bars represent ± 1 standard error of the mean at each time point. Abbreviations: VS = ventral striatum; IPL = inferior parietal lobule; iPCS = inferior precentral sulcus; and sPCS = superior precentral sulcus.

Table 2
Regions observed during cue (correct trials only) that showed significant interaction effects

| Talairach coordinates | | | Region | BA | Effect | F | P | Volume (mL) |
|-----------------------|-----|-----|--------------------------------|-------|-----------------------|------|-------|-------------|
| x | y | z | | | | | | |
| 14 | 2 | -7 | Right VS* | ** | $A \times T$ | 3.08 | 0.023 | 270 |
| -10 | 2 | -4 | Left VS** | ** | $A \times T$ | 3.20 | 0.027 | 135 |
| 26 | -13 | 53 | Right SPS** | 6 | $I \times T$ | 2.70 | 0.05 | 486 |
| 44 | 11 | 32 | Right inferior frontal gyrus** | 6, 9 | $I \times T$ | 4.47 | 0.006 | 459 |
| -28 | -64 | 41 | Left precuneus** | 19, 7 | $I \times T$ | 2.96 | 0.036 | 891 |
| -28 | -52 | 38 | Left IPL** | 7 | $A \times I \times T$ | 3.40 | 0.021 | 891 |

Note: Single asterisk indicates that interaction is across 13 estimated time points, double asterisks indicate that interaction is across TRs 3-6. Abbreviations: $A \times T$ = age by time interaction, $I \times T$ = incentive by time interaction, and $A \times I \times T$ = age by incentive by time interaction.

(Fig. 5), adolescents compared with adults had greater evoked activity for both incentive trial types. Across TRs 3-6, a significant incentive condition by age by time interaction was still present for this region ($F(3,96) = 4.143$, $P = 0.008$).

Table 5 provides the location of peak voxels for all functional clusters observed in a priori anatomical regions demonstrating significant modulation across time during the response preparation epoch.

Epoch 3: Saccade Response

Reward-Related Regions

During the saccade response epoch, the left OFC (-25, 44, -4) showed an age by time interaction ($F(3,96) = 4.44$, $P = 0.006$) (Fig. 6, left). This region showed heightened activity primarily in adolescents during neutral trials. No significant activation was observed in the VS during the saccade-response epoch.

Oculomotor and Inhibitory Control Regions

The right anterior cingulate, BA 24, (2, 23, 26) showed an incentive by time interaction ($F(3,96) = 3.99$, $P = 0.010$) (Table 6). As in the OFC cluster above, time courses from this region showed heightened activity primarily in adolescents during neutral trials. A region in the left anterior cingulate gyrus, BA

Table 3

Regions demonstrating a main effect of time in anatomical ROIs, observed during cue (correct trials only).

| Talairach coordinates | | | Region | BA | Peak F | Volume (mL) |
|-----------------------|-----|-----|---|--------|--------|-------------|
| x | y | z | | | | |
| 5 | 50 | 11 | Right MFG/VMPFC | 10, 32 | 6.38 | 810 |
| 35 | 47 | 8 | Right middle frontal gyrus, lateral OFC | 10 | 4.36 | 432 |
| 35 | 41 | -4 | Right middle frontal gyrus, lateral OFC | 47, 11 | 3.71 | 189 |
| 35 | 23 | -16 | Right inferior frontal gyrus, lateral OFC | 47 | 5.4 | 486 |
| 32 | 32 | -7 | Right inferior frontal gyrus, lateral OFC | 47, 11 | 4.12 | 270 |
| -4 | 53 | 20 | Left superior/MFG | 9, 10 | 6.49 | 864 |
| -7 | 50 | 8 | Left MFG, VMPFC | 10, 32 | 8.71 | 810 |
| -28 | 32 | -1 | Left inferior frontal gyrus, lateral OFC | 47 | 3.3 | 217 |
| -37 | 44 | 8 | Left middle frontal gyrus | 10, 46 | 3.18 | 81 |
| -19 | 53 | 2 | Left superior frontal gyrus | 10 | 3.97 | 270 |
| 8 | 32 | 2 | Right rostral anterior cingulate, VMPFC | 24, 32 | 7.86 | 729 |
| 8 | 41 | 8 | Right rostral anterior cingulate, VMPFC | 32, 10 | 6.41 | 783 |
| 2 | 17 | 32 | Right dorsal anterior cingulate | 32, 24 | 3.48 | 270 |
| -1 | 29 | 17 | Left dorsal anterior cingulate | 24, 32 | 6.28 | 702 |
| -7 | 41 | 2 | Left rostral anterior cingulate, VMPFC | 32 | 5.98 | 810 |
| -1 | 35 | 8 | Left rostral anterior cingulate, VMPFC | 24, 32 | 5.91 | 837 |
| -13 | 8 | 38 | Left cingulate gyrus | 32, 24 | 5.13 | 432 |
| 38 | -10 | 44 | Right superior precentral sulcus | 6 | 5.91 | 783 |
| 35 | -1 | 41 | Right superior precentral sulcus | 6 | 5.86 | 729 |
| 41 | 2 | 29 | Right inferior frontal gyrus | 6 | 4.7 | 486 |
| -34 | -4 | 35 | Left inferior frontal gyrus | 6 | 6.69 | 756 |
| -25 | -10 | 50 | Left superior precentral sulcus | 6 | 6.63 | 864 |
| -34 | -7 | 50 | Left superior precentral sulcus | 6 | 5.63 | 324 |
| -46 | -7 | 38 | Left inferior precentral sulcus | 6 | 3.33 | 162 |
| -4 | -1 | 53 | Left MFG | 6 | 10.29 | 810 |
| 29 | -61 | 38 | Right precuneus | 7 | 14.05 | 891 |
| 29 | -52 | 32 | Right precuneus | 39 | 10.31 | 837 |
| 41 | 32 | 14 | Right DLPFC | 46 | 4.71 | 675 |

24, 32, (-1, 11, and 35) showed a significant age by incentive by time interaction ($F(12,384) = 2.860, P = 0.037$) across the entire estimated response. Time courses from the left anterior cingulate (Fig. 6, bottom left) showed an initial peak in adults during reward trials and a similar response in adolescents during neutral trials. Adolescents showed a greater negative-going response during reward trials. Across TRs 3–6, a significant age group by time interaction ($F(3,96) = 4.474, P = 0.006$) remained for this region.

Extensive activity was observed elsewhere in the a priori oculomotor control regions in both age groups during the saccade-response epoch, including sPCS, posterior parietal cortex, and putamen (Table 7) that did not show significant interactions of age or incentive (Fig. 6, right).

Discussion

We used fast, event-related fMRI to examine developmental differences in reward-system activation, and effects of reward contingency on oculomotor inhibitory control as healthy adolescents and adults performed a monetary incentive-mediated AS task. Although behavioral performances improved in both age groups on reward relative to neutral trials, several differences were found in the patterns of BOLD responses during different epochs or stages of reward processing. Most notably, adolescents, compared with adults, demonstrated attenuated responses in the VS during the incentive cue, followed by a heightened response in the VS and sPCS during response preparation (reward anticipation) on reward trials. This increased activity during response preparation may have contributed to significant improvements in adolescent correct response rates, as will be discussed in more detail below.

Developmental Differences in Reward Contingency Effects on AS Behavior

Compared with the neutral condition, trials with a reward contingency were associated with an improved ability to correctly inhibit (adolescents) and make quicker responses (adolescents and adults). These results are consistent with previous behavioral work showing decreased error rates with reward contingency in adults and adolescents during rewarded AS tasks (Duka and Lupp 1997; Jazbec et al. 2005, 2006; Hardin et al. 2007) and suggest that essential components of the circuitry supporting reward modulation of inhibitory control are on-line by adolescence. Our results also suggest that adolescents may be particularly sensitive to reward modulation of inhibitory control, given that adolescents, but not adults, showed a significant improvement in correct response rate. However, we cannot be confident based on the eye data alone that adolescent performance is more sensitive to reward given that a significant age group by incentive-type interaction was not observed. It may be the case that adults were already performing the task at a high level during neutral trials and that there may not have been as much room for improvement on reward trials (i.e., ceiling effect). Future work could further explore differences in sensitivity to rewards by increasing the difficulty of the rewarded AS task (e.g., by shortening the duration of the preparatory period). Further, although adolescents' poorer performance on neutral trials may be attributable to relative immaturity in inhibitory control, it is also possible that adolescents did not find the neutral trials as "rewarding" as did adults. In other words, adults may have been more motivated to perform well regardless of incentive type, whereas the adolescents may have paid particular attention only to trials where a reward was at stake. Future work comparing adolescent and adult behavior on trials with neutral cues as well as reward and loss/punishment cues that parametrically vary in magnitude is needed to provide more insight on this issue.

Both adolescents and adults generated faster correct ASs (lower latencies) on reward compared with neutral trials, reflecting motivational effects of potential monetary reward on endogenously driven saccades (Roesch and Olson 2004; Hikosaka et al. 2006). The latency data reported here are in line with previous nonhuman primate studies demonstrating that saccades to rewarded (vs. nonrewarded) locations have reduced latencies, a result of heightened contralateral neuronal activity levels in basal ganglia prior to eye movement responses (Hikosaka et al. 2006). Furthermore, the latencies of AS errors were also faster on reward versus neutral trials in adolescents but did not differ in the adult group. The observation that adolescents have faster latencies during reward versus neutral-error trials further hints that adolescents may be more sensitive to reward contingencies; this heightened reactivity to rewards may contribute to enhanced impulsivity during adolescence.

Taken together, the behavioral results indicate that reward incentive improves overall inhibitory control (i.e., correct response rate) and decreases saccadic-reaction time in both adolescents and adults.

Reward Contingency Effects on Brain Responses in Adolescence versus Adults

Although adolescents recruited a largely similar neural network as adults throughout the task, including the VS, sPCS, IPL, and

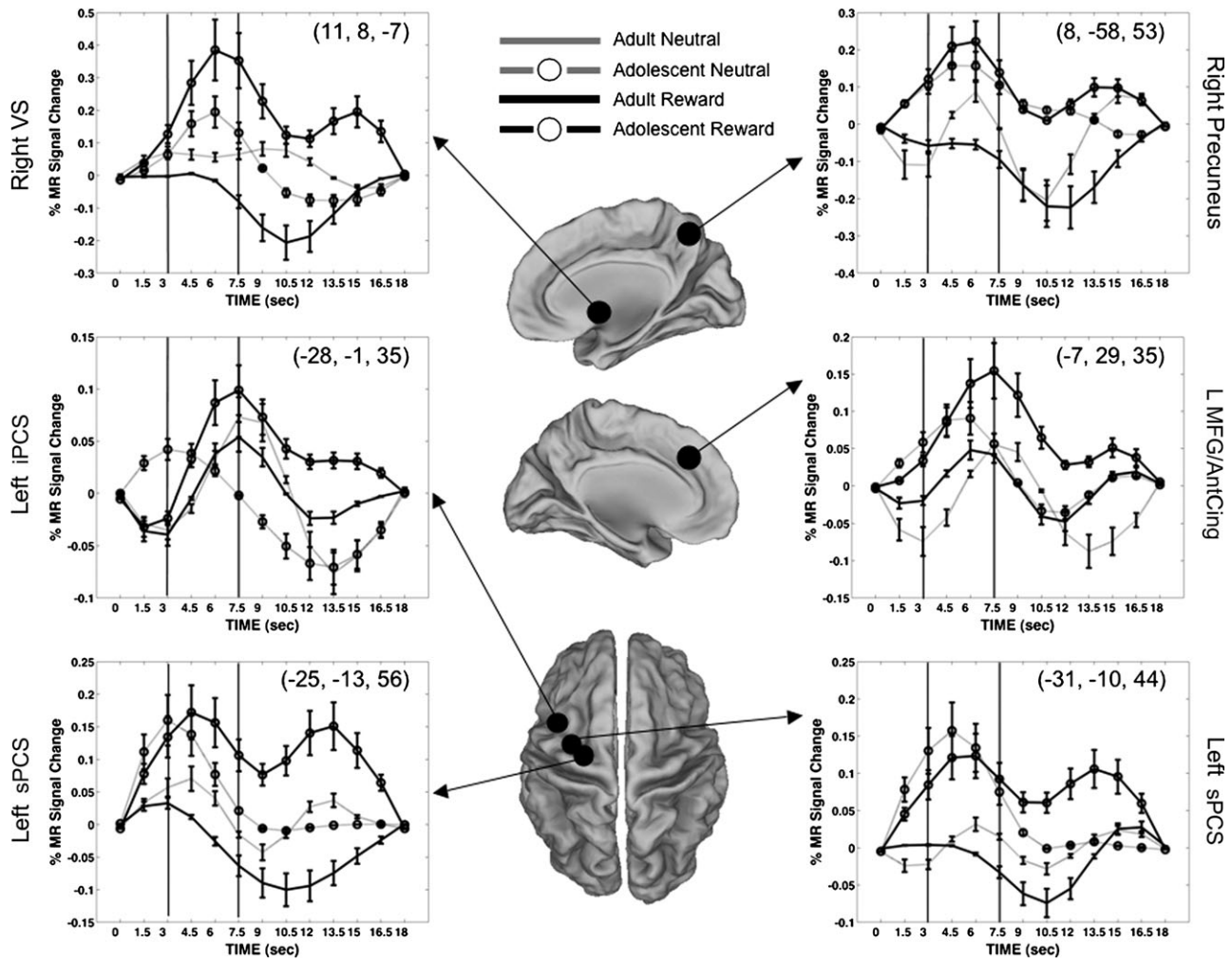


Figure 5. Response preparation (reward anticipation) time courses showing age and/or incentive interactions across time. Time courses were extracted from a sphere mask (9-mm diameter) centered on coordinates of peak voxel (see Materials and Methods). For visualization purposes only, filled black circles indicating the location of masks are schematically shown above the surface of the Human PALS atlas, drawn using Caret (version 5.5). (Note that the black circles shown here do not reflect the actual shape of mask.) As indicated in legend, solid black line = adult response during reward trials; solid gray line = adult response during neutral trials; solid black line with circular markers = adolescent response to reward trials, solid gray line with circular markers = adolescent response to neutral trials. Error bars represent ± 1 standard error of the mean at each time point. Abbreviations: VS = ventral striatum; iPCS = inferior precentral sulcus; sPCS = superior precentral sulcus; and MFG = medial frontal gyrus.

Table 4
Regions observed during response preparation (correct trials only) that showed significant interaction effects

| Talairach coordinates | | | Region | BA | Effect | <i>F</i> | <i>P</i> | Volume (mL) |
|-----------------------|----------|----------|------------------------------------|-------|-----------------------|----------|----------|-------------|
| <i>x</i> | <i>y</i> | <i>z</i> | | | | | | |
| 11 | 8 | -7 | Right ventral striatum* | ** | $A \times T$ | 2.59 | 0.05 | 216 |
| -7 | 29 | 35 | Left MFG/anterior cingulate** | 8, 32 | $A \times I \times T$ | 3.84 | 0.012 | 135 |
| 17 | -10 | 53 | Right MFG/superior frontal gyrus** | 6 | $A \times T$ | 2.92 | 0.038 | 135 |
| -25 | -19 | 47 | Left superior precentral sulcus** | 6 | $A \times I \times T$ | 2.92 | 0.038 | 297 |
| -25 | -13 | 56 | Left superior precentral sulcus* | 6 | $A \times I \times T$ | 2.89 | 0.032 | 324 |
| -31 | -10 | 44 | Left superior precentral sulcus** | 6 | $A \times I \times T$ | 2.91 | 0.038 | 270 |
| -28 | -1 | 35 | Left inferior precentral sulcus** | 6 | $A \times I \times T$ | 3.28 | 0.024 | 135 |
| 8 | -58 | 53 | Right precuneus* | 7 | $A \times T$ | 3.09 | 0.024 | 648 |

Note: Single asterisk indicates that interaction is across 13 estimated time points, double asterisks indicate that interaction is across TRs 3-6. Abbreviations: $A \times T$ = age by time interaction and $A \times I \times T$ = age by incentive by time interaction.

middle frontal gyrus, there were distinct developmental differences in activation during separate epochs of the task. Two major patterns of age group differences were observed: 1) regions where adolescents showed different recruitment for reward trials than adults, suggesting immaturities in reward processing and 2) regions where adolescents showed greater recruitment across incentives, supporting previous findings of immaturities in inhibitory control. These differences will be discussed in more detail in the following sections:

Notably, across the trial epochs, we observed bilateral clusters of activation in the sPCS near the junction with the superior frontal sulcus, an area repeatedly suggested to be the human homolog of the monkey FEF (Luna et al. 2001; Curtis and Connolly 2008). Single-unit recordings from nonhuman primates have demonstrated that FEF neurons are active during the response preparation period of AS trials and increase toward when a saccade is generated (Bruce and Goldberg 1985; Hanes and Schall 1996; Munoz and Everling 2004). Given that the clusters of activation near sPCS found in the present study were indeed active during the preparatory period and

Table 5

Regions demonstrating a main effect of time in anatomical ROIs, observed during response preparation (correct trials only)

| Talairach coordinates | | | Region | BA | Peak <i>F</i> | Volume (mL) |
|-----------------------|----------|----------|--|--------|---------------|-------------|
| <i>x</i> | <i>y</i> | <i>z</i> | | | | |
| 2 | 62 | 14 | Right superior frontal gyrus, medial OFC | 10 | 4.1 | 270 |
| 8 | 35 | -4 | Right rostral anterior cingulate, VMPFC | 24, 10 | 4.04 | 162 |
| 8 | 14 | 35 | Right dorsal anterior cingulate | 32, 24 | 9.24 | 810 |
| 11 | 2 | 44 | Right dorsal anterior cingulate | 24 | 3.78 | 189 |
| 5 | 29 | 32 | Right dorsal anterior cingulate | 32 | 3.24 | 108 |
| 26 | -10 | 44 | Right superior precentral gyrus | 6 | 5.16 | 432 |
| 35 | -4 | 44 | Right superior precentral sulcus | 6 | 4.36 | 486 |
| 29 | -10 | 53 | Right superior precentral sulcus | 6 | 3.93 | 189 |
| -22 | -1 | 56 | Left superior frontal gyrus | 6 | 4.22 | 216 |
| -16 | -13 | 53 | Left MFG/superior frontal gyrus | 6 | 3.52 | 189 |
| 5 | 2 | 56 | Right MFG | 6 | 6.28 | 702 |
| 29 | -61 | 35 | Right precuneus | 39 | 7.46 | 837 |
| -25 | -61 | 44 | Left superior parietal lobule | 7 | 9.92 | 837 |
| -10 | -61 | 56 | Left superior parietal lobule | 7 | 4.29 | 378 |
| -46 | 35 | 11 | Left inferior frontal gyrus | 46 | 4.56 | 378 |
| 20 | 29 | 35 | Right middle frontal gyrus | 8 | 4.07 | 216 |
| -25 | 35 | 35 | Left middle frontal gyrus | 9 | 3.57 | 135 |

again during the saccade response (see Supplementary Figures) and that the reported clusters were spatially near the clusters identified using similar oculomotor paradigms (AS, visually-guided, and memory-guided saccade tasks) in previous studies from our laboratory (Luna et al. 1998, 2001; Geier et al. 2007, 2009) and others (Paus 1996; Sweeney et al. 1996; Brown et al. 2004; Curtis and Connolly 2008), we cautiously conclude that the reported sPCS clusters of activation near the junction with the superior frontal sulcus (BA 6) are likely the human homolog of the monkey FEF.

Similarly, activation along the dorsomedial wall near the dorsal part of the paraCS (BA 6) has been reliably associated with eye movements (Grosbras et al. 1999) and is frequently referred to as the supplementary eye field (SEF) (Luna et al. 2001; Brown et al. 2004). The cortex immediately rostral to a vertical line extending from the anterior commissure, adjacent to the putative SEF, is frequently referred to as presupplementary motor area (Luna et al. 2001; Curtis and D'Esposito 2003). In the remaining sections, we refer to these regions by their putative functional designations as a means to

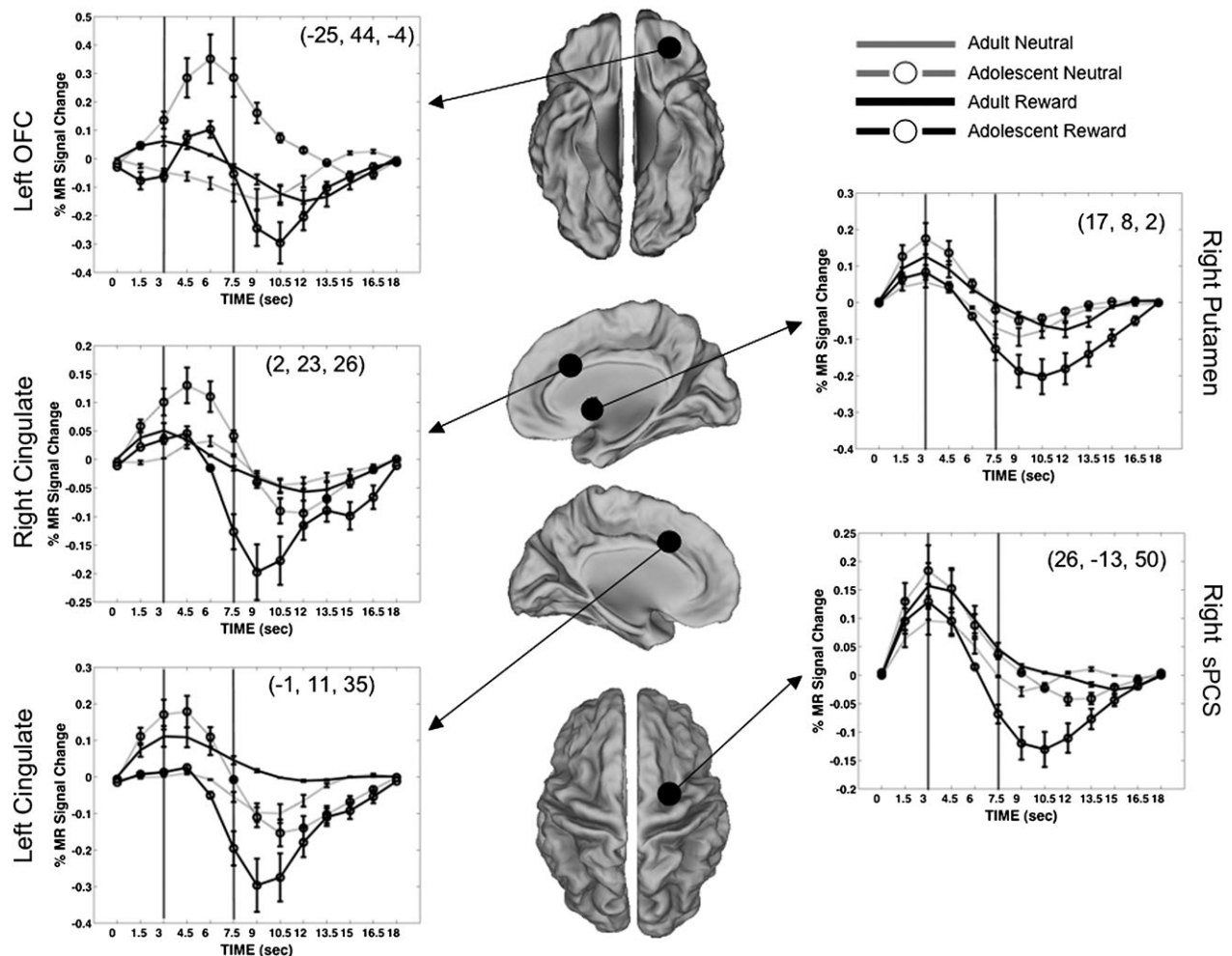


Figure 6. Saccade response epoch time courses showing age and/or incentive interactions across time. Time courses were extracted from a sphere mask (9-mm diameter) centered on coordinates of peak voxel (see Materials and Methods). For visualization purposes only, filled black circles indicating the location of masks are schematically shown above the surface of the Human PALS atlas, drawn using Caret (version 5.5). (Note that the black circles shown here do not reflect the actual shape of mask.) As indicated in legend, solid black line = adult response during reward trials; solid gray line = adult response during neutral trials; solid black line with circular markers = adolescent response to reward trials, solid gray line with circular markers = adolescent response to neutral trials. Error bars represent ± 1 standard error of the mean at each time point. Abbreviations: OFC = orbitofrontal cortex and sPCS = superior precentral sulcus.

Table 6

Regions observed during saccade response (correct trials only) that showed significant interaction effects

| Talairach Coordinates | | | Region | BA | Effect | F | P | Volume (mL) |
|-----------------------|----|----|--|--------|-----------|------|-------|-------------|
| x | y | z | | | | | | |
| -25 | 44 | -4 | Left middle frontal gyrus, lateral OFC** | 11 | A × T | 4.44 | 0.006 | 378 |
| 2 | 23 | 26 | Right cingulate gyrus** | 24 | I × T | 3.99 | 0.010 | 837 |
| -1 | 11 | 35 | Left cingulate gyrus* | 24, 32 | A × I × T | 2.86 | 0.037 | 891 |

Note: Single asterisk indicates that interaction is across 13 estimated time points, double asterisks indicate that interaction is across TRs 3-6. Abbreviations: A × T = age by time interaction, I × T = incentive by time interaction.

Table 7

Regions demonstrating a main effect of time in anatomical ROIs, observed during saccade response (correct trials only)

| Talairach coordinates | | | Region | BA | Peak F | Volume (mL) |
|-----------------------|-----|----|---|--------|--------|-------------|
| x | y | z | | | | |
| 5 | 38 | -7 | Right rectal gyrus, medial OFC | 10, 11 | 6.84 | 810 |
| -4 | -1 | 44 | Left cingulate gyrus, dorsal medial PFC | 24 | 7.22 | 783 |
| -1 | -4 | 32 | Left cingulate gyrus, dorsal medial PFC | 24 | 3.48 | 189 |
| 26 | -13 | 50 | Right superior precentral sulcus | 6 | 15.63 | 891 |
| 41 | 5 | 47 | Right middle frontal gyrus | 6 | 10.99 | 864 |
| 47 | 11 | 35 | Right inferior frontal gyrus | 6 | 8.4 | 864 |
| 32 | 2 | 32 | Right inferior frontal gyrus | 6 | 6.64 | 675 |
| 23 | 20 | 44 | Right superior frontal gyrus | 8, 6 | 5.17 | 594 |
| 11 | 11 | 50 | Right superior frontal gyrus | 6 | 4.89 | 459 |
| 20 | 11 | 47 | Right superior frontal gyrus | 6 | 4.83 | 621 |
| -22 | -16 | 53 | Left superior precentral sulcus | 6 | 12.39 | 864 |
| -28 | -1 | 44 | Left middle frontal gyrus | 6 | 5.67 | 567 |
| -28 | 8 | 53 | Left middle frontal gyrus | 6 | 4.54 | 540 |
| -34 | -1 | 29 | Left inferior precentral sulcus | 6 | 4.01 | 270 |
| 2 | -10 | 59 | Right MFG, paracentral sulcus | 6 | 8.71 | 810 |
| -7 | -10 | 62 | Left MFG, paracentral sulcus | 6 | 11.02 | 810 |
| 14 | -49 | 44 | Right precuneus | 7 | 4.04 | 513 |
| 11 | -82 | 32 | Right cuneus | 19, 18 | 10.38 | 864 |
| 35 | -67 | 32 | Right angular gyrus | 39 | 5.96 | 837 |
| 47 | -67 | 38 | Right IPL | 39 | 5.92 | 594 |
| 35 | -49 | 44 | Right IPL | 40, 7 | 3.98 | 432 |
| 47 | -37 | 41 | Right supramarginal gyrus | 40 | 4.01 | 216 |
| -43 | -70 | 38 | Left precuneus | 18, 39 | 6.83 | 567 |
| 17 | 8 | 2 | Right putamen | ** | 18.9 | 891 |
| 47 | 26 | 23 | Right middle frontal gyrus | 45, 46 | 6.93 | 891 |
| 41 | 17 | 26 | Right middle frontal gyrus | 9, 46 | 6.31 | 864 |
| -43 | 23 | 26 | Left middle frontal gyrus | 9, 46 | 5.64 | 594 |

facilitate comparisons between our results, the extant neuroimaging literature, and the rich nonhuman primate oculomotor and reward literatures.

Developmental Differences in Reward-Cue Assessment

During the presentation of the incentive cue (ring of dollar bills or pound signs), when the valence of the incentive cue was initially assessed (i.e., when the subject determined whether the forthcoming trial was to be a reward “gain” or neutral “no gain” trial), adults and adolescents showed a differential response in the VS. The VS has been consistently implicated in functional imaging studies during the anticipatory processing of rewards, including initial reward detection, prediction, and anticipation (Knutson and Cooper 2005). Adolescents showed an initial negative-going response that was nearly identical for reward and neutral trials (Fig. 4) indicating that the valence of the cue was not being differentially processed. In contrast, adults showed activity in the right VS during the reward cue that showed some differentiation from neutral cues, suggesting that the reward cue was being evaluated.

Furthermore, a later peak was observed near the end of the estimated response for both reward and neutral trials in adults but not in adolescents.

The observed BOLD signal changes in the adult and adolescent VS might be related to the dynamics of DA signaling (Knutson and Gibbs 2007). Nonhuman primate studies have demonstrated that DA neurons, which originate in the midbrain and prominently project to the dorsal and ventral striatum and PFC, phasically respond to rewards and reward-predicting stimuli (Schultz 1998) and, as such, would likely be active in response to the presentation of the incentive cues in this study. Moreover, some DA neurons have been shown to have phasic activations followed by depressions in response to novel or intense stimuli (Schultz et al. 1993; Schultz 2002). Thus, the attenuated response profiles observed in adolescents could reflect that the incentive cue was initially more motivationally salient or intense for the adolescents. In adults, although the underlying neuronal mechanisms contributing to the later occurring peak are not known and must be interpreted cautiously, one possible contributing factor could be slow, tonic firing of DA neurons, which can occur across extended time scales (Schultz 2002; Knutson and Gibbs 2007). This mechanism, which could be useful to maintain motivational processing during extended times, may not yet be mature by adolescence. Conceivably, these different response patterns in adults and adolescents might be related to changes in the density and distribution patterns of different DA receptor subtypes occurring with age (Seeman et al. 1987; Meng et al. 1999; Spear 2000).

Oculomotor and control regions were recruited across incentives for adults and for rewards in adolescents in response to the incentive cue (Fig. 4). During neutral trials, however, adolescent responses in these regions were clearly attenuated (recall that only correct trials were included in time-course analyses). Given that adolescents generated overall more errors during neutral trials and had slower initiation times during correct neutral trials, these results suggest that without incentive adolescents show reduced recruitment of regions that are known to support AS performance (Everling et al. 1997; Connolly et al. 2002; Curtis and D’Esposito 2003). Increased activity during reward trials in prefrontal regions including the putative FEF, known to support oculomotor response planning (Curtis and D’Esposito 2003), suggests that these frontal regions may mediate quick, correct inhibitory responses in adolescents. Moreover, adult responses to the reward cue, particularly in left IPL and right iPCS, were temporally extended relative to the adult neutral response and to adolescent activity. Each of these regions has been previously implicated in various aspects of oculomotor and/or attentional control (Gitelman et al. 1999; Cabeza and Nyberg 2000; Luna et al. 2001; Brown et al. 2004), especially in response preparation (Connolly et al. 2002; Curtis and Connolly 2008). Increased engagement of these regions during reward cues likely reflects that potential gains are more attentionally salient to both age groups, unsurprisingly, which probably contributes to their faster response latencies and higher correct response rates. Rewards may have a greater relative effect on attention and performance in adolescents relative to adults given that adolescents show weak early responses in these regions during neutral trials but increased participation during reward trials. Adolescents still do not perform the AS task as well as adults do (Fischer et al. 1997; Munoz et al. 1998; Klein and Foerster 2001) indicating that it is more difficult for

them to voluntarily inhibit a response. Because of this greater difficulty in cognitive control, adolescents may rely on prefrontal executive systems to support improved performance in a similar manner to adults who demonstrate increased reliance on prefrontal systems when the cognitive load is increased (Keller et al. 2001).

Developmental Differences in Reward Anticipation/Response Preparation

During the response preparation/reward anticipation epoch (red fixation cross), when subjects presumably anticipated responding for a reward or for no gain (neutral), we found that adolescents, but not adults, showed robust activity in the VS during reward trials (Fig. 5 top left). This result suggests hyperactivity during anticipation of a reward in adolescents compared with adults. Our results demonstrating a relative overactive VS function during response preparation but underactive (negative-going) function earlier during the initial presentation of the incentive cue, may speak to an on-going issue in the reward literature regarding hyper versus hypofunctionality of the adolescent reward system (Spear 2000; Chambers et al. 2003; Ernst et al. 2006). For example, Bjork et al. (2004) found that adolescents underactivate the VS relative to adults during a period when subjects anticipate responding for a reward, supporting a hypofunctionality hypothesis. In contrast, Ernst et al. (2005) and Galvan et al. (2006) (when reward magnitude was high), for example, showed that adolescents “over”activate this region in response to receiving a reward, supporting hyperfunctionality. Our data indicate that the adolescent VS can show “both”: an initial dip in activity in response to incentive cues, which could be interpreted as relative underactivity, followed by a distinct hyperactive response to reward anticipation. The results reported here inform what appear to be contradictory findings in the literature and indicate that there may be different developmental trajectories for temporally different stages of anticipatory reward processing.

Although the mechanism underlying the activity pattern observed in adolescent VS cannot be directly determined from this study, heightened DA signaling is a potential contributing factor. Converging evidence from rodent and primate models indicate an overall increase in DA levels during adolescence (Seeman et al. 1987; Kalsbeek et al. 1988; Rosenberg and Lewis 1994, 1995; Meng et al. 1999; for a review see Spear 2000), which, in conjunction with a different constellation of DA receptor subtypes (Seeman et al. 1987; Meng et al. 1999; Spear 2000) and a likely overall abundance of synapses in the striatum (Sowell et al. 1999), may contribute to 2 different forms of a heightened reward response, negative-going activity in response to the incentive cue (reflecting heightened salience of reward) and positive-going responses during response preparation (reflecting heightened expectation of receiving a reward) (Cooper and Knutson 2008).

Adolescents also showed increased recruitment of putative FEF compared with adults during the preparatory period for both neutral and reward trials. This suggests that adolescents initially recruit FEF more than adults in preparing to perform a correct inhibitory response regardless of reward incentive. Importantly, adolescents also showed temporally prolonged responses during reward trials in the putative FEF as well as MFG/anterior cingulate (Fig. 5). Nonhuman primate studies have demonstrated that a preparatory build-up of activity levels

in FEF “fixation” neurons contribute to successful inhibition of a saccade toward the peripheral target in the AS task, perhaps by tonically inhibiting saccade-generating motor neurons (Schall et al. 2002; Munoz and Everling 2004). Neurons in anterior cingulate have been shown to carry multiple signals, including one related to the anticipation and delivery of reinforcement (Schall et al. 2002). We hypothesize that the increased activation we observed in putative FEF may reflect an increase in fixation-related neuronal activity that then contributes to the improvements in adolescent performance (correct response rates) by enhancing response preparation. Furthermore, heightened anticipatory signals in the VS and anterior cingulate during reward trials may contribute to enhanced signal in the putative FEF, which in turn could exert an even greater top-down influence on saccade-related neurons in caudate and superior colliculus (Ding and Hikosaka 2006; Hikosaka et al. 2006). Future single-unit studies will be needed to examine these proposed mechanisms.

In any case, the data presented here further indicate that the neural mechanisms underlying reward-cue identification and anticipation are widely distributed (e.g., cingulate, FEF, and basal ganglia) (O’Doherty et al. 2004) and immature during adolescence. It has been widely suggested that during adolescence, a normative imbalance exists between reward- and cognitive control-related brain regions, which likely exposes vulnerabilities to risk taking (Steinberg 2004; Ernst et al. 2006; Galvan et al. 2006; Casey et al. 2008). It may be that mature reward-motivated control of behavior, and the emergence of consistent, adult-like adaptive decision making, rests on the functional integration of multiple brain regions including PFC (Luna et al. 2004).

Developmental Differences in Response/Reward “Feedback”

During the saccade response, most of the regions recruited did not show significant group or incentive by time interactions (Table 7; Fig. 6, right). However, adolescents strongly recruited a region in the left lateral OFC during neutral trials that was not significantly engaged by adults (Fig. 6, top left). The OFC has been implicated in numerous aspects of reward processing (Kringelbach and Rolls 2004), including coding representations of incentive valence and magnitude during reward feedback (Delgado et al. 2000, 2003). Lateral OFC in particular has been associated with punishing/negative outcomes (O’Doherty et al. 2001). Although subjects were not given explicit feedback in this task based on their performance, they did demonstrate evidence for intrinsic feedback when a mistake was made. That is, subjects reliably followed incorrect ASs with corrective saccades toward the appropriate location, indicating that they knew they had made a mistake (Velanova et al. 2008). Adolescents also showed differential responses primarily during neutral trials in bilateral dorsal anterior cingulate (Fig. 6, middle and bottom left). One suggested role of dorsal anterior cingulate is in monitoring behavioral outcome (Ridderinkhof, Ullsperger, et al. 2004). It may be that for adolescents, the tangible outcome of correctly performed neutral trials, where money is neither earned or lost, is more ambiguous, and perhaps negative, than reward-trial outcome and is signaled by activation of OFC and dorsal anterior cingulate. Future work focused on activation evoked by explicit error feedback during reward contingent behavior

may help to clarify the roles of OFC and dorsal anterior cingulate during the saccade response in this task.

Conclusions

The current findings indicate that reward contingency contributes to improved response inhibition in adolescents and adults as indicated by increased rates of correct responses and decreased latencies of correct ASs. We provide initial fMRI evidence of increased activity during reward trials in adolescent VS and putative FEF during the response preparation epoch that may support observed AS behavioral enhancements. Further, we also demonstrate in a single experiment that adolescents may show a negative-going response in VS during reward cue assessment, then overactivate VS later during response preparation compared with adults, suggesting persistent immaturities in a key node of the adolescent reward system that could be interpreted as reflecting both an under and overactive reward system. Considered together, these results have important implications for current theoretical models of adolescent risk taking. For example, a recently proposed triadic model (Ernst et al. 2006) posits that a normative imbalance occurs during adolescence between a hyperactive reward-driven system (e.g., VS-mediated) and limited harm-avoidant (e.g., amygdala-mediated) and regulatory/executive control (e.g., PFC-mediated) circuitries. In this model, adolescents are hypothesized to engage in risk taking due to the combination of reward hypersensitivity and limited processes that control its influence on behavior. Our results suggest that rewards may “enhance” inhibitory control systems particularly during adolescence and thus are seemingly at odds with the triadic model. However, it may be that during adolescence, behaviors leading to immediate reward are enhanced at the expense of longer-term pay-offs. In the context of this controlled experiment, inhibiting a saccade leads to goal acquisition (i.e., a monetary reward) and thus the enhanced activity in VS and putative FEF was adaptive. In a nonlaboratory setting, when deciding between 2 alternatives (e.g., driving fast for the thrill vs. driving slower to avoid an accident), immaturities in reward system function may bias inhibitory control/decision making toward an action leading to a proximal reward (e.g., driving fast) and expose vulnerability to negative outcome (Steinberg et al. 2009).

In summary, our results demonstrate developmental differences in brain activation in key nodes of reward and inhibitory control circuitry during distinct trial components of a rewarded AS task. Our findings indicate that key determinants of goal-directed behavior and decision making, reward and cognitive control systems, have not yet reached mature levels of function by adolescence, potentially contributing to the emergence of risk taking in this age group.

Supplementary Material

Supplementary material can be found at: <http://www.cercor.oxfordjournals.org/>.

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