INCENTIVE PROCESSING AND INHIBITORY CONTROL IN ADOLESCENTS AND YOUNG ADULTS

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Adolescents are known to demonstrate normative increases in risk-taking behaviors. Understanding the interaction between incentive (reward, punishment) processing and basic cognitive control abilities, both of which are still maturing into adolescence, may provide insight on the basic mechanisms contributing to this complex behavioral phenomenon. In this dissertation, we present a compilation of papers aimed at characterizing the influence of potential reward gain or loss on response inhibition performance and supporting brain circuitry in adolescents and adults. In study 1, we use fast, event-related functional magnetic resonance imaging (fMRI) to examine the neural circuitry supporting perfomance on an antisaccade task with reward or neutral contingencies added to each trial. Results indicate that components of the adolescent reward system exhibit an initially sluggish, then eventually overactive response to rewards, as well as limited recruitment in regions supporting the executive assessment of rewards. In study 2, the effects of different magnitudes of potential gains and losses on antisaccade task performance were examined. Results indicate that higher compared to lower magnitude reward contingencies differentially affect adolescent, but not adult, response suppression abilities. Furthemore, both age groups performed consistently well (low error rates) on punishment trials. In study 3, adolescents and adults underwent fast, event-related fMRI as they performed a rewarded antisaccade task with fixed-magnitude reward and punishment stimuli, previously determined to result in equivalent levels of behavioral performance across the

age groups (study 2). Additionally, auditory, performance-based feedback was provided on each trial. fMRI results indicate that during detection of reward cues, adolescents do not show the same early recruitment of oculomotor control regions evident in adults. Furthermore, adolescents demonstrated temporally extended responses in several brain regions (e.g., orbitofrontal cortex, supplementary eye field) during the preparatory period of potential punishment trials, reflecting possible immaturities in mechanisms underlying potential loss or 'risk' anticipation. Finally, adults demonstrated enhanced activity in the ventral striatum and cortical eye fields during the response/feedback epoch, suggesting more mature consummatory processing. Collectively, the results of these studies demonstrate protracted development of higher-order executive aspects of reward processing and its interaction with response inhibition abilites into adolescence.

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PREFACE

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1.0 INTRODUCTION

Adolescence is widely recognized as a time of peak novelty and sensation seeking, behaviors supported by immature reward-related brain circuitry (Steinberg, 2004). Components of cognitive control, including response inhibition (also known as response suppression), are also known to exhibit protracted maturation into adolescence (Luna et al., 2004; Klein & Foerster, 2001). Immature incentive (reward, punishment) processing coupled with limited cognitive control may contribute to poor decision-making and ultimately risk taking behaviors, a major health concern for this age group (Arnett, 1992; Dahl 2004, Steinberg, 2004). While we know that components of the cognitive control of behavior continue to improve through adolescence, we have limited understanding about developmental changes in the reward/motivation system and about the interaction of these two systems during this stage of development. *The primary objectives of this dissertation are to better characterize how rewards and punishments are represented in the adolescent brain relative to young adults and examine the influence of incentives on response inhibition, a primary component of the cognitive control of behavior.*

We begin by reviewing our current understanding of mature and immature reward processing, aspects of cognitive control, and brain maturation (Chapter 2). Also in this review, we examine a basic model in which the interaction of still-maturing reward processing and inhibitory control is suggested to be a primary component underlying poor decision-making associated with risk-taking. In chapters 4 through 6, we expound on this model by presenting

data from three studies each addressing specific developmental questions related to the behavioral and neural responses elicited during rewarded antisaccade (inhibitory control) tasks. In study 1, we use fast, event-related fMRI and scanner eye tracking data to characterize the neural circuitry underlying temporally dissociable stages of incentive processing and response inhibition in adolescents and adults as they perform a novel, monetary incentive antisaccade task. In study 2, we use behavioral eye tracking to characterize the influence of different magnitudes of rewards and punishments on key behavioral indices of response suppression, as well as introduce measures intended to minimize differences in incentive value across age groups. In study 3, we use fast, event-related fMRI to examine the neural circuitry engaged during reward and punishment anticipatory processing, as well as circuitry recruited during auditory performance-based feedback. Additionally, for study 3 we use incentive stimuli found to result in equivalent behavioral performance across age groups. Finally, the results from all three studies are synthesized and implications of this work in the context of our basic model are discussed.

Two chapters in this dissertation have been submitted for publication. A modified version of chapter 2 has been accepted and is currently in press, with primary author Charles Geier and co-author Beatriz Luna. A modified version of chapter 4 (study 2) has also been submitted and is currently under review, with primary author Charles Geier and co-authors Robert Terwilliger, Theresa Teslovich, Katerina Velanova, and Beatriz Luna.

2.0 THE MATURATION OF INCENTIVE PROCESSING AND COGNITIVE CONTROL

Adolescence refers to the developmental time period between childhood and adulthood, generally considered to encompass ages 12-17 in humans, taking into account variability in factors such as puberty and gender (Spear, 2000; Dahl, 2004). In parallel with obvious pubertal changes (e.g., increases in height, weight, and secondary sex characteristics), a number of characteristic behaviors emerge during adolescence, including heightened sensation- and novelty-seeking and increased behavioral impulsivity (Arnett, 1992; Spear, 2000). These changes appear to be highly conserved behavioral traits, as they have been observed across cultures and even species (Spear, 2000; Laviola, Macri, Morley-Fletcher, & Adriani, 2003). Normative increases in these behaviors have been proposed to serve an adaptive function in that they promote exploration of the environment and the development of skills necessary for independence in adulthood (Kelley, Schochet, & Landry, 2004). However, such behaviors, particularly when coupled with immature cognitive control abilities, may increase the likelihood of engaging in risky and reckless behaviors, which can undermine survival (Zuckerman, 1979; Arnett, 1992; Spear, 2000; Zuckerman, 1994). Risk-taking is broadly defined here as engaging in behaviors that may be high in subjective desirability (i.e., associated with high sensation, novelty, or perceived reward) but exposes the individual to potential injury or loss. Examples of risk-taking include initiating use of addictive drugs, driving at excessive speeds, and engaging in

unprotected sex (Arnett, 1992; Silveri, Tzilos, Pimentel, & Yurgelun-Todd, 2004; Dahl, 2004). Negative outcomes associated with adolescent risk taking are a major health concern for this age group (Spear, 2000; Dahl, 2004), resulting in dramatic increases in mortality rates despite peaks in other measurable aspects of physical health (Resnick et al., 1997; Call et al., 2002; Dahl, 2004).

A primary component of heightened sensation/novelty seeking and risk taking in adolescence is immature brain circuitry mediating incentive (reward, punishment) processing (Arnett, 1992; Spear, 2000; Chambers, Taylor, & Petenza, 2003; Ernst, Pine, & Hardin, 2006). Immaturities in incentive-related brain circuitry could, for example, lead to misevaluation of the value or predicted consequences associated with a given stimulus or action thereby biasing decision-making. As an example, an adolescent with a still-maturing incentive processing system might decide that jumping his/her skateboard down a steep flight of stairs is highly rewarding, particularly if friends are watching, while not giving equal weight to the associated risk (e.g., the severe pain associated with a broken ankle) as might most adults. Thorough characterization of the neurodevelopment of the reward system could advance our understanding of adolescent risky behaviors and inform educational and intervention strategies for this age group (Dahl, 2004). In addition, our understanding of the etiology of various mood and substance abuse disorders would be informed by the characterization of incentive processing during adolescence. Schizophrenia, depression, and substance abuse disorders, for instance, often emerge during the adolescent years (Sweeney, Takarae, Macmillan, Luna, & Minshew, 2004; Everling & Fischer, 1998; Chau, Roth, & Green, 2004) and often exhibit co-morbid abnormalities in incentive processing (Chau et al., 2004).

Yet, the normative maturation of incentive-related brain circuitry through adolescence is just beginning to be investigated in humans. Current data indicate that adolescents process incentives differently than adults, although the nature and directionality of such differences has not yet been fully characterized (Chambers et al., 2003; Ernst et al., 2006; Spear, 2000) (discussed below). Furthermore, a mechanistic understanding of the interaction of adolescent incentive processing and other functional networks likely contributing to risk taking is currently under-specified. That is, while immature incentive processing expectedly plays a primary role in these behaviors, additional functional brain systems including those mediating core aspects of cognitive control are critically intertwined and need to be jointly considered.

Below, we review the literature on the maturation of incentive processing and basic components of cognitive control as an initial step towards generating a clearer understanding of normative adolescent behavior and vulnerabilities to risk taking. We begin by highlighting two broad theoretical models that posit how adolescent incentive processing differs from adults. We then provide well-characterized evidence describing primary elements of the adult reward system, followed by a review on what is currently known regarding the adolescent system. A description of brain maturation and cognitive development follows in order to provide an overall picture of the collective limitations that affect the motivation and decision-making systems during adolescence.

2.1 MODELS OF ADOLESCENT INCENTIVE PROCESSING

Two models emerge from the adolescent reward literature which characterize how incentive processing is different in adolescents compared to adults, and how such processing may contribute to risk-taking (Spear, 2000; Chambers et al., 2003; Ernst et al., 2006). Both models agree that adolescents recruit a similar underlying brain circuitry and that there is a fundamental difference in the way that the adolescent brain processes incentives relative to adults. The models diverge, however, in terms of the directionality of this difference.

One model suggests that the adolescent incentive processing system is *hypo*-active relative to adults and results in reduced motivation (Spear, 2000). In other words, those brain areas that process incentives are not recruited as strongly or to the same degree as they are in adults given equivalent reward contingency. In this model, risk-taking is explained as adolescents seeking out experiences with high reward values because those with more modest value are not sufficiently appetitive or enticing enough to drive a normatively under-active reward system, specifically the ventral striatum (VS, which includes the nucleus accumbens) (Spear, 2000). As a consequence, adolescents may be more vulnerable to drug addiction, for example, because they require quantitatively more drug per use to drive a hypo-responsive reward system. This model shares general similarity to accounts of adult dopamine (DA) hypo-function (Spear, 2000) and a model of ADHD (Castellanos & Tannock, 2002) (see below).

In contrast, a second model suggests that adolescents are *hyper*-responsive to incentives. That is, adolescents demonstrate a heightened sensitivity to rewards and over-activate incentive-related brain circuitry compared to adults given the same reward contingency (Chambers et al., 2003; Ernst et al., 2006). Chambers and colleagues (2003), for example, point out that normative maturational increases in monoaminergic (dopamine) neurotransmitter activity in the fronto-

striatal 'motivational' system compared to relatively lower levels of inhibitory (e.g., serotoninergic) mechanisms contributes to increased reward sensitivity in adolescents (Chambers et al., 2003). In typical development, increased activity in motivational circuitry serves an important adaptive function in that it leads to adolescents engaging in novelty and sensation-seeking behaviors which may promote independent skills necessary for survival in adulthood (Kelley et al., 2004). However, this increased activity could also confer vulnerability in adolescents in the form of a heightened sensitivity in risk taking behaviors such as on the dependency producing effects of addictive drugs.

Hyper-active incentive processing is also central to a proposed triadic model of adolescent risk taking (Ernst et al., 2006). This model suggests that during adolescence a normative imbalance exists between a hyperactive reward-driven system (e.g., ventral striatum-mediated) and limited harm-avoidant (e.g., amygdala-mediated) and regulatory/executive control (e.g., prefrontal cortex-mediated) circuitries. Behaviorally, adolescents are more 'reward-driven' (i.e., respond more strongly to rewards than adults) due to the combination of reward hyper-sensitivity and limited processes that control its influence on behavior. The triadic model shares similarities with the model suggested by Chambers et al. (2003) in that there is an imbalance in reward and inhibitory circuitries during adolescence and that increased sensitivity to rewarding stimuli is hypothesized, particularly in the ventral striatum. The triadic model is novel in terms of emphasizing the notion of functional interconnectivity among multiple related circuitries, including executive control, to explain risk-taking.

The hypo- and hyper-active reward system models lead to seemingly contrasting predictions of neural activation and behavior in adolescents. In the following sections, we examine how the adolescent reward system may demonstrate *both* over- and under-active

responses to a reward. We begin with a brief overview of the reward processing in adults as this establishes a useful framework for studying the adolescent system.

2.2 ADULT INCENTIVE PROCESSING

Incentive processing in the mature brain is supported by a relatively well-delineated circuitry. Single-cell studies in non-human primates have demonstrated that incentives modulate neuronal activity in several regions, including the dorsal and ventral striatum (nucleus accumbens, NAcc), midbrain (ventral tegmental area, substantia nigra pars compacta), amygdala, orbito-, medial, and lateral prefrontal cortex, and posterior parietal cortex (Apicella, Ljungberg, Scarnati, & Schultz, 1991; Hikosaka, Nakumura, & Nakahara, 2006; Schultz, 2000; Roesch & Olson, 2003; Wise, 2002; Roesch & Olson, 2004). Neuroimaging studies in humans have identified similar regions in adults (Thut et al., 1997; O'Doherty, 2004; McClure, York, & Montague, 2004; Delgado, Nystrom, Fissell, Noll, & Fiez, 2000; Knutson, Westdorp, Kaiser, & Hommer, 2000; Breiter, Aharon, Kahneman, Dale, & Shizgal, 2001; Delgado, Locke, Stenger, & Fiez, 2003; Elliott, Newman, Longe, & Deakin, 2003).

Importantly, the temporal resolution afforded by single-cell and event-related functional magnetic resonance imaging (fMRI) studies have lead to the observation that specific brain regions carry temporally distinct information or 'signals' related to rewards (Schultz, Tremblay, & Hollerman, 2000; O'Doherty, 2004). Figure 1 schematically represents a sample of these reward-related signals, brain regions identified as subserving them, and their temporal relation with respect to incentive delivery. In this model, incentive signals are broadly categorized as those occurring prior to or after incentive delivery. Distinguishable signals occurring *prior* to

incentive delivery include reward detection, as well as estimation of the valence (i.e., positive valence is equated with reward/gain and eliciting approach behavior, negative valence is equated with loss/punishment and eliciting avoidance behavior) and anticipated value of a future incentive (O'Doherty, Diechmann, Critchley, & Dolan, 2002; Knutson & Cooper, 2005). The term 'value' is inconsistently defined in the literature and often used inter-changeably with 'expected value', the magnitude of a reward times the probability of its attainment (Schultz, 2004). In this dissertation, value is conceptualized as a complex interaction between an incentive's magnitude (i.e., amount of reward available) (Leon & Shadlen, 1999; Roesch et al., 2004; Wallis & Miller, 2003; Delgado et al., 2003), probability of attainment (O'Doherty, 2004), the time between action and incentive delivery (Tsujimoto & Sawaguchi, 2005), an animal's state of satiety (Critchley & Rolls, 1996), and subjective preference (Tremblay & Schultz, 1999; Hassani, Cromwell, & Schultz, 2001). Signals occurring *after* incentive delivery include, for example, those related to the magnitude and valence of the received incentive (Delgado et al., 2003; Delgado et al., 2000; Rolls, 2000; O'Doherty, Kringelbach, Rolls, Hornak, & Andrews, 2001), as well as those corresponding to whether or not the outcome matched up with predictions ('prediction error' signals) (Schultz, 2000; Schultz & Dickenson, 2000; Hare, O'Doherty, Camerer, Schultz, & Rangel, 2008).

Importantly, several brain regions including the OFC, VS, and aspects of the medial prefrontal cortex are consistently engaged and support computations that underlie these multiple incentive signals. For example, regions in the OFC have been implicated in executive assessment of rewards including representations of subjective preference and valence (Hare et al., 2008; Kringelbach, 2005), while the ventral striatum (VS) contributes to anticipatory processing, including initial reward detection and prediction (Knutson et al., 2005) as well as prediction error

signaling (O'Doherty et al., 2003). Thus, characterizing how these regions develop, in particular, is central to understanding limitations in specific aspects of reward system function during adolescence and will be a primary focus of this dissertation.

The discernable signals and the temporal nature of reward processing observed in adults form a useful framework in which to consider the adolescent reward system, which is discussed next.

2.3 ADOLESCENT INCENTIVE PROCESSING

In contrast to the extensive literatures exploring the neural basis of mature incentive processing in non-human primates and human adults, fewer studies have specifically focused on the development of this system through adolescence in humans (May et al., 2004; van Leijenhorst, Crone, & Bunge, 2006; Bjork, Smith, Danube, & Hommer, 2007; Bjork et al., 2004; Ernst et al., 2005; Eshel, Nelson, Blair, Pine, & Ernst, 2007; Galvan et al., 2006). Collectively, studies indicate that adolescent incentive processing is supported by a similar neural circuitry as adults, including orbitofrontal cortex, basal ganglia (dorsal and ventral striatum, including nucleus accumbens), amygdala, and medial prefrontal cortex. However, as will be illustrated below, the manner in which these regions are recruited by adolescents differs during the temporal course of incentive processing.

May et al. (2004) found that children and adolescents recruit ventral striatum and orbital frontal cortex (similar to non-human primate reports) during the anticipation of reward or loss in a gambling task. This study was the first to apply event-related functional neuroimaging methods to child and adolescent incentive processing, but did not have an adult comparison group

undermining the ability to make developmental comparisons of activity in primary reward processing regions. Studies which have investigated developmental differences between adolescents and adults in incentive processing have focused on different temporal aspects of incentive processing, leading to disparate conclusions. For example, Bjork et al. (2004) compared blood oxygenation level dependent (BOLD) changes during an anticipatory period (i.e., before responding to receive incentive) in adolescents and adults using the monetary incentive delay (MID) task (Knutson et al., 2000), a rewarded reaction time task. Briefly, in this task subjects first saw one of several geometric shapes, each of which was uniquely associated with a different magnitude of reward (money) available at trial end. Subjects then fixated a white crosshair for a variable delay period (i.e., the 'anticipation' period) after which they had to quickly respond via button press when a white square was flashed on the screen. If subjects responded while the square was still visible, they earned the promised reward. While adolescents performed similarly to adults on this task (by design), adolescents exhibited significantly less activation compared to adults in the right ventral striatum (nucleus accumbens, NAcc) and extended-amygdala while anticipating responding for a reward (versus a condition where no reward was available). Ernst et al. (2005) using fMRI examined changes in the BOLD response as subjects performed a rewarded decision-making task—the 'wheel of fortune' task. In this task, subjects had to choose via button press which half of a colored wheel they thought would be randomly picked by the computer (referred to as the 'choice' epoch). Each colored side was associated with a different magnitude of reward (win money) or punishment (lose money). Following a brief anticipation phase, subjects were presented with feedback about what color the computer selected (unbeknownst to the subjects, the color choice was selected at random but at a predetermined probability) and what incentive they received. During this feedback epoch (i.e.,

consummatory processing), adolescents demonstrated enhanced activity in the left nucleus accumbens, whereas adults exhibited more activity in the left amygdala, suggesting that adolescents are more sensitive to rewards (associated with NAcc) and adults are more sensitive to punishments (associated with amygdala) (Ernst et al., 2006). Subsequent work manipulated the probability of receiving a reward by changing the relative size of the colored wheel slices in the Wheel of Fortune task (Eshel et al., 2007). In this study, BOLD activity unique to the 'choice' epoch was investigated. Although behavioral performance did not differ across ages, adults activated OFC/VLPFC (BA 47, 10) and dorsal ACC (BA 32) significantly more than adolescents when making risky selections. These regions are known to contribute to aspects of cognitive control (Fuster, 1997), as well as the monitoring and resolution of conflicting decisions (Carter et al., 1998). Results thus indicate that adolescents do not engage prefrontal regulatory mechanisms as much as adults when making risky choices. In a more recent study, Bjork and colleagues (2007) investigated the circuitry supporting rewarded decision-making using a novel monetary game of 'chicken' in which subjects had to choose when to bank accumulating rewards before the trial unpredictably terminated. Trials varied in terms of the penalty associated with losing (failing to bank winnings before trial stopped). During the reward accrual (anticipation) component of the task, adolescents activated posterior mesofrontal cortex, a region reported to be recruited during pre-response conflict and during the monitoring and avoidance of errors (Ridderinkhof, Ullsperger, Crone, & Nieuwenhuis, 2004), in a similar manner compared to adults in cases when a severe threat of loss was clear. However, under milder and more ambiguous conditions of risk, adolescents under-activated this region. Similarly, children (9 to 12 year-olds) compared to adults (18-26 year-olds) were found to recruit the anterior cingulate cortex more during high risk decision-making and engaged lateral orbitofrontal cortex more in

response to negative compared to positive feedback (van Leijenhorst et al., 2006). These results suggest that younger subjects have limitations in prefrontally guided cognitive aspects of reward assessment that may underlie their apparent under-activity of rewards when valence is harder to assess.

Galvan et al. (2006) using fMRI investigated BOLD differences in subjects performing a rewarded match-to-sample paradigm. Briefly, subjects saw one of three different visual cues (pictures of cartoon pirates) presented to the left or right of fixation, each of which was associated with a distinct reward value (different amounts of money). Following a brief delay, subjects saw two images of treasure chests to the left of right of fixation and were instructed to select (via button press and within 2 seconds) which chest appeared on the same side as the previous pirate picture. Subjects were then given feedback indicating if and how much they had won. Across the whole trial, adolescents demonstrated an exaggerated response (higher magnitude of BOLD response) in NAcc relative to children or adults during the reward receipt epoch for large rewards. Furthermore, the extent (number of significantly active voxels) of NAcc activity in adolescents looked more like adults than children, overall. In OFC, adolescents looked more like children in terms of both extent and magnitude of activation. Results from this study were interpreted as reflecting a protracted development of OFC relative to NAcc and suggest that adolescents have limitations in the executive assessment of rewards and an overactive reward system.

Collectively, the studies above suggest that the predictions of the hypo- and hyper-active models may not be mutually exclusive. For instance, Bjork et al. (2004) found under-activity in ventral striatum during a period when adolescents *anticipated responding* for rewards. This is a temporally distinct phase of incentive processing than that explored by Ernst et al. (2005) and

Galvan et al. (2006), studies which report adolescents had increased activity during periods including reward *receipt*. Thus, an important factor contributing to the hypo- versus hyper-active distinction may be the temporal stage of incentive processing under scrutiny—that is, distinct phases of incentive processing result in different patterns of activations which may have different developmental trajectories.

Interestingly, Bjork et al. (2004) did not observe significant differences in the ventral striatum between adolescents and adults performing the MID task during reward receipt, an epoch more directly comparable with Ernst et al. (2005). One factor that may underlie these contradictory results is a difference in the levels of cognitive load demanded by the different tasks. Bjork et al. (2004) used a simple reaction time task where subjects simply responded to the appearance of a target, while the paradigms used by Galvan et al. (2006) and Ernst et al. (2006) required that subjects assess different responses and invoke working memory for instructions and past performance. More cognitively demanding tasks have been shown to recruit additional brain areas and/or increased activity within a single area (Rubia et al., 2000) and may increase the likelihood of recruiting reward-related brain areas.

Finally, we note that conclusions based on studies that compare BOLD responses across different age groups are a common concern. The challenge put forth by neuroscientists investigating the adult system is that it is not straightforward if BOLD activity changes in fMRI studies are due to actual differences in neuronal computations or an isolated artifact due to immaturities in the vasculature or gross head size differences. Counter to these arguments, however, we note that brain size is adult-like by early childhood (see Brain Maturation during Adolescence, below) and that the feasibility of comparing BOLD responses across developmental age groups transformed into a common stereotaxic space has been well

established (Brown et al., 2005; Kang, Burgund, Lugar, Petersen, & Schlagger, 2003; Wenger, Visscher, Miezin, Petersen, & Schlaggar, 2004). An additional concern is that performance differences in the scanner by different age groups are what primarily contribute to different levels or patterns of BOLD activity. We agree that this may be an effect in some studies; however, pediatric imaging studies frequently employ simple tasks easily performed by children (e.g., oculomotor tasks) by design (Luna, Garver, Urban, Lazar, & Sweeney, 2004a; Galvan et al., 2006) minimizing performance differences while still observing functional differences. Furthermore, when performance is equated across age groups (Bjork et al., 2004; Schlaggar et al., 2002), age-related functional differences are also still observed.

Below, we next address *why* adolescents may demonstrate these particular patterns of functional brain activity—that is, what underlying brain mechanisms support these types of responses? From adolescence to adulthood, important brain structural and physiological changes continue to occur with significant effects on brain function. Differences in brain maturational state, including thinning gray matter (e.g., synaptic pruning), increases in white matter (e.g., myelination), and neurotransmitter system differences, likely contribute to the particular functional patterns observed in adolescents and adults and are examined below.

2.4 BRAIN MATURATION DURING ADOLESCENCE

Overall size, weight, cortical folding, and regional functional specialization of the human brain is adult-like by early childhood (Armstrong, Schleicher, Omran, Curtis, & Zilles, 1995; Caviness, Kennedy, Bates, & Makris, 1996; Giedd et al., 1996a; Giedd et al., 1996b; Reiss, Abrams, Singer, Ross, & Denckla, 1996). While basic aspects of brain development are in place early, key

processes continue to refine the basic structure to fit the biological and external environments. Two such processes include synaptic pruning and increased myelination (Huttenlocher, 1990; Jernigan, Trauner, Hesselink, & Tallal, 1991; Pfefferbaum et al., 1994; Giedd et al., 1999b), which are critical to the developmental progression of the functional integration of frontal regions with the rest of the brain (Thatcher, Walker, & Giudice, 1987; Luna & Sweeney, 2004b; Chugani, 1998). These processes enhance neuronal processing and support mature cognitive control of behavior (Luna et al., 2004a).

2.4.1 Age-Related Gray Matter Reductions

Recent structural imaging studies with large subject pools indicate continued, non-linear reductions in gray matter through adolescence in cortical areas (Gogtay et al., 2004; Toga, Thompson, & Sowell, 2006; Paus et al., 1999; Sowell et al., 1999a; Giedd et al., 1999a), as well as the basal ganglia (Sowell, Thompson, Holmes, Jernigan, & Toga, 1999b). Such reduction in gray matter is largely due to the loss of weak or unused synapses via synaptic pruning (though other maturational processes such as glial cell changes, dendritic arborization, and vascular changes also contribute to this decline)(Gogtay et al., 2004). Synaptic pruning promotes enhanced information processing capacity, speed, and overall efficiency and supports complex computations within regional circuitry.

Gogtay and colleagues (2004) demonstrated a progressive decline of gray matter density throughout neocortex with increasing age. Notably, higher-order 'association' cortical areas including orbitofrontal cortex, dorsolateral prefrontal cortex, and the lateral temporal lobes, show persistent decreases in gray matter volume through adolescence (Gogtay et al., 2004). Evidence from post-mortem histological studies also confirm a protracted rate of regional gray matter

reduction with age that differs by region (Huttenlocher, 1990). For example, the middle frontal gyrus in prefrontal cortex continues to mature into adolescence, as opposed to visual cortex, which stabilizes near adult levels during childhood (Huttenlocher, 1990).

The basal ganglia (including dorsal and ventral striatum) and prefrontal areas, notably the orbitofrontal and dorsolateral prefrontal cortex, demonstrate comparably late maturation (Sowell et al., 1999b; Gogtay et al., 2004; Giedd, 2004). Protracted maturation in these areas may have important ramifications for incentive processing during adolescence. As mentioned above, these regions underlie multiple incentive-related signals in adults. Immaturities in these areas would thus be expected to result in a limited ability to efficiently and accurately form representations of key signals like incentive valence and value. Furthermore, immaturities in the OFC and dorsal and ventral striatum would be expected to affect an adolescent's ability to generate reliable predictions of incentive outcome and perhaps feedback-based learning computations.

2.4.2 Age-Related White Matter Increases

Myelination refers to the increase in fatty insulation surrounding neuronal tracts. Myelination enhances the efficiency of information processing by increasing the speed and fidelity of distal neuronal transmission, aiding the functional integration of widely distributed circuitry, critical for the emergence of complex cognitive behavior (Goldman-Rakic, Bates, & Chafee, 1992; Luna et al., 2004b). Myelination increases in a linear fashion throughout development and occurs in parallel to the non-linear gray matter reductions described above (Yakovlev & Lecours, 1967). Similar to findings regarding gray matter, myelination does not occur last in frontal regions but throughout the brain. Frontal, temporal and parietal association areas continue to myelinate through adolescence compared to earlier maturation in occipital regions. Recent studies using

diffusion tensor imaging (DTI), which indirectly measures the integrity of white matter of which myelination is a primary contributor, substantiate previous histological work and, collectively, indicate a continued increase in measures of frontal white matter anisotropy throughout childhood and into adulthood, evidence for continued white matter integrity (myelination) with age (Klingberg, Vaidya, Gabrieli, Moseley, & Hedehus, 1999; Barnea-Goraly et al., 2005; Mukherjee & McKinstry, 2006; Huppi & Dubois, 2006).

As noted above, a distributed yet limited number of brain areas are known to consistently activate during incentive processing, including spatially distant regions like the orbitofrontal cortex, basal ganglia (dorsal and ventral striatum/nucleus accumbens), amygdala, and lateral prefrontal cortex. The inter-connectivity of these brain regions has been well characterized (Alexander, DeLong, & Strick, 1986; Middleton & Strick, 1994; Middleton & Strick, 2000; Middleton & Strick, 2002; Carmichael & Price, 1995; Haber, Kunishio, Mizobuchi, & Lynd-Balta, 1995; Haber, Fudge, & McFarland, 2000; Groenewegen, Wright, & Uylings, 1997). Importantly, accumulating evidence in human and animal studies suggests that pathways within and between these regions are not yet fully myelinated during adolescence. For example, Klingberg and colleagues (1999) demonstrated with DTI that fiber tracts throughout frontal cortex continue to myelinate well into the second decade of life. In another study, Olesen and colleagues (2003) combined DTI (structural) and fMRI (functional) analyses in 8-18 year olds and demonstrated that enhanced integrity of connections between superior frontal sulcus, inferior parietal lobe, and caudate were found to correlate with BOLD response and visual-spatial working memory performance. The Olesen et al. study importantly links brain structure with function, supporting the notion that increased myelination of pathways contributes to improved working memory abilities (Luna et al., 2004a; Demetriou, Christou, Spanoudis, & Platsidou,

2002). Similarly, Liston and colleagues (2006) demonstrated that enhanced integrity of fronto-striatal tracts correlated with improved performance on a go/no go task and with age. The fronto-striatal tract is a crucial communication route for top-down cognitive control mechanisms like response inhibition as well as incentive processing. Converging evidence of continued myelination in the developing brain also comes from the animal literature. For example, amygdalo-cortical pathways in rat continue to myelinate through adolescence (Benes, Turtle, Khan, & Farol, 1994). The progressive maturation of amygdalo-cortical pathways could provide one plausible mechanism for increasingly more inhibitory control affecting reward processing with age.

A normatively under-myelinated brain (relative to adults) would be expected to undermine adolescents' ability to have efficient and rapid access to incentive signals as well as limit how rapidly these signals may be integrated and used to inform decision-making and guide behavior. Further, given that the overall value of an incentive is complex and may emerge from different computational processes (e.g., magnitude, delay to receipt, etc.), and that evidence suggests that these components are coded by distributed brain areas, accurate value representations, in particular, may rest on efficient functional connectivity between regions aided by myelination. Importantly, immature myelination would also make top-down, prefrontal cortex mediated cognitive control mechanisms like response inhibition (Liston et al, 2006) inefficient (see below) and may confer vulnerability to impulsive behaviors.

In addition to brain structural changes, important changes occur in key neurotransmitter systems during adolescence. Evidence for on-going changes in dopamine signaling during adolescence will be briefly considered next.

2.4.3 Maturation of Dopamine Signaling

Dopamine (DA), a key monoamine neurotransmitter modulating reward circuitry (Kirsch et al., 2006), has been associated with multiple aspects of reward processing, including the hedonic value associated with rewards, motivation, and the reinforcement of rewarded behavior (Wise, 2004). Dopamine cells primarily originate from the zona compacta of the substantia nigra and the ventral tegmental area (VTA) and are known to project to components of the basal ganglia (nigrostriatal system), the limbic system, including hippocampus, amygdala, and nucleus accumbens (mesolimbic system), as well as to widespread areas of the frontal lobe (mesocortical system). Converging evidence from human and animal models indicates that the mechanisms underlying dopamine neurotransmission in striatal and cortical systems continue to mature during adolescence in a number of ways (Spear, 2000; Andersen, 2003; Crews, He, & Hodge, 2007). For example, human nigrostriatal DA neurons show the highest tyrosine hydroxylase (the rate limiting enzyme in dopamine synthesis) activity in childhood, followed by an exponential decrease during the next first three decades of life (Segawa, 2000). In rat striatum, D1 and D2 receptors levels are greater during adolescence compared to adulthood (Seeman et al., 1987). In addition to changing receptor levels, activity levels appear to change as well, with D1 and D2 receptor binding in the rat striatum peaking during adolescence (post-natal day 40) at levels that are 30-40% greater than in adults (Seeman et al., 1987; Spear, 2000). The density of dopamine transporters, which function to remove DA from the synapse, has also been shown to peak during adolescence in the striatum (Meng, Ozawa, Itoh, & Takashima, 1999). Furthermore, evidence indicates that during adolescence, there is relatively greater activity in dopamine systems than in inhibitory serotonin (5-HT) systems, potentially resulting in an imbalance in reward (DA-mediated) and suppression (5-HT-mediated) mechanisms (Takeuchi et al., 2000;

Lambe, Krimer, & Goldman-Rakic, 2000; Ernst et al., 2006; Spear, 2000). In mesocortical pathways, non-human primate work has shown that DA inputs to prefrontal cortex (PFC) peak in adolescence (Rosenberg & Lewis, 1994; Rosenberg & Lewis, 1995; Spear, 2000). In rats, DA fiber density to PFC also increases in adolescents relative to adults (Kalsbeek, Voorn, Buijs, Pool, & Uylings, 1988). Taken together, these studies indicate heightened DA processing during adolescence which may have significant effects on reward processing.

Developmental changes in dopamine signaling may provide insight on the functional differences observed between adolescent and adult incentive processing. First, as noted above while there is an overall increased in DA input, there is a peak in the number of dopamine transporters (DAT) in adolescence, which function to remove DA from the synapse. An increase in the number of transporters could lead to limitations in the ability to maintain motivation over a delay or anticipation period compared to adults. Indeed, a recent model of attention deficit hyperactivity disorder (ADHD) suggests that the premature removal of synaptic DA may lead to impairment in the ability to sustain motivation for a delayed reward (Castellanos et al., 2002). As a behavioral consequence, short-term rewards may be favored over long-term rewards in individuals with ADHD (Krain & Castellanos, 2006) as well as in healthy adolescents (albeit to a lesser degree). A peak in DAT resulting in normative limitations sustaining motivation induced by a reward across an anticipatory delay may help explain adolescents' decreased activity in the nucleus accumbens as indicated in Bjork et al. (2004). Second, as demonstrated by Segawa (2000), nigrostriatal DA neurons and components of the basal ganglia show higher activity during adolescence than adulthood. Increased dopaminergic activity, coupled with thicker gray matter (and perhaps more synapses) in adolescents compared to adults (Sowell et al., 1999b), may partially explain adolescents' enhanced response in the nucleus accumbens to the receipt of

a reward as indicated in Ernst et al. (2005), particularly when there is no delay before receiving it (and thus the increased transporters are not a factor).

2.5 MATURATION OF COGNITIVE CONTROL

Risk taking behavior not only involves reward assessment but cognitive control, both of which contribute to decision making (Sugrue, Corrado, & Newsome, 2005). In parallel with functional changes in reward processing and on-going structural and neurotransmitter differences, aspects of cognitive control also show protracted development through adolescence. The maturation of these cognitive control processes, including working memory and voluntary response suppression, may play significant roles in how incentives guide behavior by regulating what incentive-related information is accessible during decision-making. The maturation of voluntary response suppression and working memory, and their proposed relations to incentive-related processing and behavior, are discussed below.

2.5.1 Maturation of Voluntary Response Suppression

Voluntary response suppression (also referred to as response inhibition) refers to the ability to inhibit task irrelevant responses to prepotent or salient stimuli in favor of goal-appropriate action. Inhibitory control is engaged when deciding among competing alternatives during decision-making (Hooper, Luciana, Conklin, & Yarger, 2004; Pierrot-Deseilligny et al., 2003). As such, this system expectedly serves an important regulatory role in incentive-based decision-making. An immature voluntary response suppression system may bias an adolescent to respond to an

immediate reward, even if that means neglecting a larger reward that is delivered later (i.e., delay discounting) (Yarkoni, Braver, Gray, & Green, 2005; Hariri et al., 2006).

A distributed neural circuitry underlies voluntary response suppression in adults, including dorsolateral prefrontal cortex (DLPFC), the cortical eye fields, anterior cingulate cortex, basal ganglia, superior colliculus, and thalamus, among others, as indicated by non-human primate electrophysiology (Munoz & Everling, 2004; Funahashi, Chafee, & Goldman-Rakic, 1993) and functional imaging work in human (Brown, Goltz, Vilis, Ford, & Everling, 2006; Luna et al., 2001; Connolly, Goodale, Menon, & Munoz, 2002; Ford, Goltz, Brown, & Everling, 2005).

Converging evidence from several studies demonstrates that inhibitory control of behavior continues to improve throughout childhood and well into adolescence. Compared to children, adolescents exhibit improved inhibitory performance during the Go-No-Go, Stroop, Flanker, and Stop signal tasks, and are able to more reliably hold fixation in the presence of visual distractors (Levin, Culhane, Hartmann, Evankovich, & Mattson, 1991; Williams, Ponesse, Schachar, Logan, & Tannock, 1999; Liston et al., 2006; Ridderinkhof, Band, & Logan, 1999; Paus, Babenko, & Radil, 1990; Luciana & Nelson, 1998; Tipper, Bourque, Anderson, & Brehaut, 1989; Ridderinkhof, van der Molen, Band, & Bashore, 1997). Studies using the antisaccade task (Hallett, 1978), which measures the ability to halt an impending saccade to a suddenly appearing stimulus, indicates continued improvements in response suppression during adolescence, with adult-like levels of control stabilizing by mid-adolescence or later (Fischer, Biscaldi, & Gezeck, 1997; Fukushima, Hatta, & Fukushima, 2000; Klein & Foerster, 2001; Luna et al., 2004a; Munoz, Broughton, Goldring, & Armstrong, 1998).

Although adolescents can appear to behave like adults on the antisaccade task, they engage a different neural circuitry to do so. Our previous developmental antisaccade fMRI study indicated that performance on the antisaccade task is supported by the establishment of a widely distributed neural circuitry that shows continued refinement through adolescence (Luna et al., 2001; Luna et al., 2004a). Adolescents rely more heavily on still-maturing regions like the dorsolateral prefrontal cortex (DLPFC), while showing reduced involvement in inhibitory/oculomotor control areas like the cortical eye fields (FEF, SEF) (Luna et al., 2001) and performance monitoring regions such as anterior cingulate (Velanova et al., 2008) These data support other studies consistently indicating protracted development of inhibitory control circuitry (Rubia et al., 2000; Durston et al., 2006; Casey et al., 1997; Rubia et al., 2006; Rubia, Smith, Taylor, & Brammer, 2007; Bunge, Dudukovic, Thomason, Vaidya, & Gabrieli, 2002; Adleman et al., 2002; Tamm, Menon, & Reiss, 2002; Marsh et al., 2006; Luna et al., 2001).

2.5.2 Maturation of Working Memory

Working memory refers to the ability to maintain and, when necessary, manipulate information on-line that is needed to have goal-directed executive behavior (Baddeley, 1983; Baddeley, 1992; Fuster, 1997). Working memory improvement throughout adolescence is important for the emergence of adult-level higher-order cognition (Nelson et al., 2000; Bjorklund & Harnishfeger, 1990); (Dempster, 1981; Dempster, 1981; Case, 1992). Immaturities in working memory would be predicted to limit adolescents' ability to maintain critical incentive related information (i.e., estimated reward value, probability of reward receipt, previous reward history, etc.), particularly when there are multiple and/or competing incentive stimuli, during decision-making.

Widely distributed brain areas are known to underlie working memory. In non-human primates, such areas include prefrontal cortex (Funahashi, Inoue, & Kubota, 1997; Funahashi, Inoue, & Kubota, 1993), frontal eye field (FEF) (Funahashi, Bruce, & Goldman-Rakic, 1989), supplementary eye field (SEF) (Hanes, Thompson, & Schall, 1995), inferior parietal lobule (Colby, Duhamel, & Goldberg, 1996; Gnadt & Andersen, 1988), caudate nucleus (Hikosaka, Sakamoto, & Usui, 1989), and substantia nigra pars reticulata (SNpr) (Hikosaka & Wurtz, 1983). Functional imaging studies with humans implicate the dorsolateral prefrontal cortex (DLPFC), FEF, SEF, inferior parietal sulcus (IPS), cingulate cortex, basal ganglia, and lateral cerebellum (Brown, Bullock, & Grossberg, 2004; Cabeza & Nyberg, 2000; Petit, Courtney, Ungerleider, & Haxby, 1998; Curtis, Rao, & D'Esposito, 2004; LaBar, Gitelman, Parrish, & Mesulam, 1999; Passingham & Sakai, 2004; Postle, Berger, Taich, & D'Esposito, 2000; Geier, Garver, & Luna, 2007; Postle, Zarahn, & D'Esposito, 2000; Sweeney et al., 1996; Wager & Smith, 2003). Non-human and human studies thus indicate that a widely distributed fronto-parietal-subcortical circuitry supports working memory.

Similar to voluntary response suppression, evidence suggests a prolonged development of working memory into adolescence (Swanson, 1999; Olesen, Nagy, Westerberg, & Klingberg, 2003; Luna et al., 2004a; Luciana et al., 1998; Demetriou et al., 2002). Performance on spatial working memory tasks, for example, where subjects must remember the location of a briefly appearing target in space, continues to improve from childhood through adolescence (Zald & Iacono, 1998; Geier, Garver, Terwilliger, & Luna, 2008; Luna et al., 2004a; Scherf, Sweeney, & Luna, 2006). Improvements in controlling interference may also contribute to increased efficiency of working memory in development (Bjorklund et al., 1990; Sakai, Rowe, & Passingham, 2002). Although adolescents recruit a more specialized network of brain regions

than children during spatial working memory tasks, they are not yet at adult levels of specificity (Scherf et al., 2006; Geier et al., 2008). Further, adolescents appear to necessitate more prefrontal activity (specifically right DLPFC) to achieve similar levels of behavioral performance (Scherf et al., 2006; Luna, Velanova, & Geier, 2008)

2.6 INCENTIVE PROCESSING, COGNITIVE CONTROL, AND PROPOSED LINKS TO RISK TAKING

Immature incentive processing is not the exclusive determinant of adolescent risk-taking. Rather, other functional circuitries including those mediating cognitive control are critically involved (Steinberg, 2004; Ernst et al., 2006). We propose that incentive-related signals and core aspects of cognitive control, specifically response inhibition and working memory, function together during decision-making[1], and that immature processing in these systems contributes to suboptimal choice behavior and, ultimately, risky behaviors (Ernst et al., 2006; Eshel et al., 2007) (Figure 2). More specifically, we propose that immaturities in dopamine neurotransmission (including increased yet short-lived DA activity, see above), as well as structural immaturities in the local circuitries (e.g., due to an abundance of under-specified synapses) and connectivity between reward-related regions (e.g., due to relatively under-myelinated pathways), could result in a sluggish but overactive reward system (once engaged)

[1] Decision-making is conceptualized here as the cognitive process of choosing one action or option over another. Each alternative is assumed to be associated with a unique set of costs and benefits.

that is biased towards shorter-term reward acquisition. These characteristics may simultaneously heighten and expose already present limitations in adolescent cognitive control systems, which are known to be less efficient (i.e., require more effort to reach adult-like performance levels) and more prone to errors (Luna et al., 2004a; Geier, Garver, Terwilliger, & Luna, 2009). The still-maturing cognitive control systems can either be enhanced by the added activation from the reward system or distracted from considering alternatives. Returning to a previous example, consider again the adolescent deciding whether or not to jump his or her skateboard down the stairs. For example, immature processing in regions like the orbitofrontal cortex, which supports executive assessment of reward value, may lead to an inflated anticipated value estimation of landing the jump relative to sustaining an injury, and thus bias the adolescent to choose to engage in the behavior. Thus, heightened responses to rewards may be a 'double-edged sword' for adolescents in that it can result in adaptive behavior if the rewarded behavior/decision at hand is appropriate (performing an innocuous choice in a scientific experiment) or potentially maladaptive behavior if the reward contingent behavior has immediate salient appeal (e.g., social approval from doing a risky skateboarding trick), despite significant longer-term risks (broken ankle).

It must be noted that risk taking is an extremely complex behavioral construct; numerous cognitive, emotional, and social processes are predicted to influence decision-making contributing to such behaviors (e.g., computational capacity, abstract thinking abilities, social context, time estimation, etc.). The basic framework proposed here is not intended to encompass all of these issues but rather focuses specifically on the influence of limited (immature) incentive processing in adolescence in the context of a still developing cognitive control system. We argue that delineating the interaction and limitations in these core elements may help us begin to

understand the fundamental mechanisms from which risk taking emerges, as well as the contributions from other functional systems. That is, if there are immaturities in the systems supporting basic aspects of reward processing and cognitive control, then the more complex aspects of reward processing would also be limited.

A primary assumption of the proposed model is that incentives should directly affect performance on tasks designed to probe working memory and inhibitory control. Further, the model suggests that adolescent and adult performance on these tasks should be differently affected, with a heightened influence of incentives on adolescent performance. Indeed, several studies indicate incentive-related modulation of performance in working memory (Krawczyk, Gazzaley, & D'Esposito, 2007) and response suppression (Duka & Lupp, 1997; Jazbec et al., 2006; Blaukopf & DiGirolamo, 2006) in adults. Moreover, studies have shown developmental differences in how rewards impact response inhibition (Jazbec et al., 2006). Using a rewarded antisaccade (AS) task, Jazbec and colleagues (2006) have shown behaviorally that adolescents and adults show decreased error rates on reward contingent AS trials. However, adolescents also demonstrated shorter antisaccade error latencies and higher peak velocities on correct rewarded trials compared to adults, who did not demonstrate modulation of these saccadic parameters in this experiment. These initial results suggest fundamental differences in the sensitivity to the effects of incentives on inhibitory behavior in adolescents compared to adults.

In next several chapters (3-5), we expound on the basic model described above and extend the adolescent reward literature by more fully characterizing how rewards and punishments are represented in the adolescent brain (relative to young adults) and by examining the influence of incentives on response inhibition, a primary component of the cognitive control of behavior.

2.7 SUMMARY AND CONCLUSIONS

Adolescence is a transitional developmental period marked by normative increases in sensation- and novelty-seeking, which can lead to maladaptive outcomes during risk taking. In this chapter, we reviewed the literature on brain systems supporting incentive processing and basic aspects of cognitive control, including working memory and response inhibition, as an initial step towards gaining insight on the neurobiological mechanisms underlying risk taking behavior. Current evidence indicates that adolescents relative to adults demonstrate under- or over-activity at different stages of reward processing, such as early hypo-responsiveness in the executive assessment and/or anticipation of rewards and later hyper-activity in consummatory responses. In parallel with these functional differences are on-going brain maturational processes like synaptic pruning and myelination, as well as key changes in dopamine neurotransmission. Moreover, there is protracted development of processes underlying cognitive control further undermining decision making affecting risk taking behavior. Finally, a simple model of adolescent risk taking was presented which emphasized the role of immature incentive processing influencing cognitive control systems during decision-making. In sum, risk-taking behavior in adolescence may best be understood as an emergent property of a still-maturing brain learning how to integrate external and internal drives.

3.0 A MODEL OF COGNITIVE CONTROL: THE OCULOMOTOR SYSTEM

In the studies presented below, the oculomotor system is used as a model system for cognitive control. Several factors guided this choice. First, oculomotor tasks are simple and can be performed successfully across multiple ages (Cohen & Ross, 1978; Ross, Radant, & Hommer, 1993). Second, oculomotor tasks are less likely to be helped by verbal or learning strategies that often overestimate developmental progression in neuropsychological tests (Chelune & Thompson, 1987). Third, the relationship of a visual stimulus to motor response is direct as opposed to paper-and-pencil and button-press tasks where transformations are applied to adapt to different modalities. Furthermore, the oculomotor system is well-suited to investigating brain/behavior relationships in the context of these studies because single cell studies in non-human primates have delineated its neurophysiology, neuroanatomy, and neurochemistry (Suzuki & Azuma, 1977; Robinson & Goldberg, 1978; Bruce, Goldberg, Bushnell, & Stanton, 1985; Bon & Lucchetti, 1990), performance on these tasks has been well documented in normal adults (Leigh & Zee, 1999) and lesion patients (Guitton, Buchtel, & Douglas, 1985; Paus et al., 1991; Henik, Rafal, & Rhodes, 1994; Pierrot-Deseilligny, Rivaud, Gaymard, Muri, & Vermersch, 1995), and the cognitive control of oculomotor behavior shows late development into adolescence (Fischer et al., 1997; Munoz et al., 1998; Fukushima et al., 2000; Klein, Foerster, Hartnegg, & Fischer, 2005; Luna et al., 2004a; Nelson et al., 2000). Moreover, reward influences on the oculomotor system have also been delineated at the single-unit level (Hikosaka,

Takikawa, & Kawagoe, 2000; Roesch et al., 2004; Roesch et al., 2003). Furthermore, as discussed above, adding a reward component to the antisaccade task has been shown to affect performance in adolescents and adults, indicating that it is particularly appropriate for investigating reward-motivated behaviors (Jazbec et al., 2006; Duka et al., 1997).

4.0 STUDY 1: REWARD PROCESSING AND EFFECTS ON BRAIN SYSTEMS UNDERLYING INHIBITORY CONTROL

4.1 INTRODUCTION

Important aspects of reward processing are still immature during adolescence contributing to limitations in decision-making such as in risk-taking behavior that characterize this period of development and impacts mortality rates (Steinberg, 2004; Arnett, 1992; Spear, 2000; Chambers et al., 2003; Ernst et al., 2006; Resnick et al., 1997; Call et al., 2002; Dahl, 2004). An extensive literature has characterized the functional neuroanatomy of reward processing in non-human primates and human adults (Schultz, 2000; Hikosaka et al., 2006; O'Doherty et al., 2001; Breiter et al., 2001; Roesch et al., 2004) identifying a circuitry including the orbitofrontal cortex, striatum, and medial prefrontal cortex (among others) as being key to reward processing (Schultz, 2000; McClure et al., 2004). Importantly, specific regions have been shown to carry temporally distinct signals about future rewards (e.g., reward detection, anticipatory processing) and received rewards (i.e., prediction errors, consummatory processing) (Schultz, 2000; Hare et al., 2008). These primary regions of the reward circuitry show persistent immaturities through adolescence including continued thinning of gray matter in basal ganglia and orbitofrontal cortex (Giedd et al., 1996b; Sowell et al., 1999b; Toga et al., 2006; Gogtay et al., 2004), and protracted maturation of efferent striatal frontal projections (Segawa, 2000) through adolescence. Dopamine

(DA) and serotonin (5-HT) systems also demonstrate immature processing compared to adults with evidence for overactivity of DA vs. 5-HT (Takeuchi et al., 2000; Lambe et al., 2000; Chambers et al., 2003; Andersen, 2005; Segawa, 2000), continued maturation of D2 receptors and DA transporters (Meng et al., 1999), and increased DA inputs to PFC (Lewis, 1997; Spear, 2000).

Initial developmental neuroimaging studies support these findings by providing evidence for immature brain mechanisms supporting reward processing in adolescence (Bjork et al., 2004; van Leijenhorst et al., 2006; Bjork et al., 2007; May et al., 2004; Eshel et al., 2007; Galvan et al., 2006; Guyer et al., 2006; Ernst et al., 2005). Evidence has been found for *under*-activity of the reward system in adolescents relative to adults during anticipatory processing in the ventral striatum (VS) and during risky decision-making in orbitofrontal cortex (OFC) and aspects of medial prefrontal cortex (Bjork et al., 2004; Eshel et al., 2007; Bjork et al., 2007), but *over*-activity in VS during reward receipt or consummatory processing (Ernst et al., 2005; Galvan et al., 2006). These results have been used to argue for and against two major theoretical models which characterize the adolescent reward system as either hyper-active (Ernst et al., 2006; Chambers et al., 2003) or hypo-active (Spear, 2000) relative to adults. Reconciliation of these opposing views is fundamental to our understanding of adolescent behavior and holds critical implications for educational and intervention strategies for this age group (Dahl, 2004).

Importantly, inhibitory control, or voluntary response inhibition, a key component of decision-making and goal-directed behavior, also shows continued improvements throughout childhood and into adolescence (Paus et al., 1990; Levin et al., 1991; Luciana et al., 1998; Tipper et al., 1989; Ridderinkhof et al., 1999). Work from our laboratory and others using the antisaccade (AS) task (Hallett, 1978), a behavioral paradigm in which subjects must inhibit a

pre-potent saccade towards a suddenly appearing peripheral target and instead endogenously generate a saccade to the mirror location, indicates that adult-like levels of inhibitory control begin to stabilize in adolescence (Munoz et al., 1998; Klein et al., 2001; Fischer et al., 1997; Luna et al., 2004a). Our previous developmental antisaccade fMRI study indicated performance on the AS task is supported by the establishment of a widely distributed neural circuitry that shows continued refinement through adolescence (Luna et al., 2001; Luna et al., 2004a). These data support other studies consistently indicating protracted development of inhibitory control circuitry (Rubia et al., 2000; Durston et al., 2006; Casey et al., 1997; Rubia et al., 2006; Rubia et al., 2007; Bunge et al., 2002; Adleman et al., 2002; Tamm et al., 2002; Marsh et al., 2006; Luna et al., 2001) including their use of errors to guide future behavior (Velanova, Wheeler, & Luna, 2008; Rubia et al., 2007). Collectively, these data suggest normative adolescent vulnerabilities in the consistency of inhibitory control.

In this chapter, we examine the neurobiological mechanisms underlying reward processing and its influence on response inhibition in healthy adolescents and adults using a novel set of approaches. We use a monetary incentive-mediated antisaccade paradigm presented in a fast, event-related fMRI design with control 'catch' trials (Ollinger, Shulman, & Corbetta, 2001b) that allows us to dissociate three reward processing stages that have been identified in the literature to be distinct (Schultz, 2000), namely reward identification, reward anticipation, and reward feedback. Moreover, we characterize the effects of reward on a component of decision-making by characterizing the effects of reward processing on inhibitory control

We hypothesized that adults and adolescents would demonstrate enhanced inhibitory control on rewarded compared to neutral antisaccade trials, as indicated by previous behavioral work (Jazbec, McClure, Hardin, Pine, & Ernst, 2005; Jazbec et al., 2006; Duka et al., 1997).

Furthermore, given evidence in the adolescent reward literature of hypo-activity during anticipatory processing (Bjork et al., 2004) and hyper-activity during consummatory processing (Ernst et al., 2005), we hypothesized that adolescents would demonstrate periods of under- *and* over-activity during reward processing depending on when during the trial the circuitry is examined, as well as recruit regions that enhance inhibitory control.

4.2 METHODS

4.2.1 Participants

Thirty-eight healthy subjects (22 adolescents, and 16 adults) were initially recruited for this study. Imaging data from four adolescents were excluded from analyses due to excessive head motion in the scanner (exclusion criteria described below). The remaining thirty-four subjects (eighteen adolescents (13-17 years old; M=15.3 (+/- 1.5); 8 females), and sixteen young adults (aged 18-30; M=21.7 (+/- 2.9); 10 females) 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 developmental work from our laboratory indicating differential behavioral performance levels on the antisaccade task (Luna et al., 2004a; 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.

4.2.2 Rewarded Antisaccade Task

During the task, subjects were initially presented with one of two incentive-indicating cues (1.5 sec) displayed at the start of each antisaccade trial (see Figure 3). A ring of green dollar bill signs ($), each subtending approximately 1 degree 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 how much actual money was at stake on each trial to avoid subjects from 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 twenty-five dollars contingent upon their performance and that no debt could be accrued (i.e., subjects could not owe money). Next, the incentive ring disappeared and the fixation cross changed from white to red (1.5 sec), indicating to the subject that they should begin to prepare to inhibit a response. Finally, a peripheral stimulus (yellow dot) appeared (75 msec) at an unpredictable horizontal location (± 3, 6, and 9 degrees 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 (1475msec).

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 inter-trial intervals (Ollinger et al., 2001b; Ollinger, Corbetta, & Shulman, 2001a). A 30% catch trial rate minimizes subjects' anticipation of a partial trial, while maintaining a sufficient frequency to allow proper estimation of the BOLD response. Two catch trial variants were presented throughout each run and consisted of the trial terminating either 1) after the response preparation period (red fixation) (i.e., no peripheral cue for the motor response was

shown), or 2) after the incentive cue images (circles of "$" or "#") (i.e., red fixation and peripheral cue were not displayed). The inter-trial fixation period was jittered between intervals of 1.5, 3, or 4.5 sec (uniformly distributed) and consisted of subjects simply fixating a central white cross presented on a black background. Inter-trial fixations followed complete trials and catch trials. 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 sec in duration. Four runs were presented per experimental session, for a total of 56 complete reward trials and 56 complete neutral trials. This is a quantitatively validated approach to estimating components within a trial (Ollinger et al., 2001b; Ollinger et al., 2001a; Goghari & MacDonald, 2008) that has been previously reported in the literature (Corbetta, Kincade, Ollinger, McAvoy, & Shulman, 2000; Brown et al., 2006; Shulman et al., 1999; Wheeler et al., 2005).

4.2.3 Eye Tracking

Subjects were tested in our behavioral laboratory within one week prior to being scanned to assure 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, USA) that recorded eye position by pupil-corneal reflection obtained by a mirror mounted on the head coil with a resolution of 0.5 degrees of visual angle. Simultaneous video monitoring was also used to assure task compliance. At the beginning of each eye-tracking session and when necessary, a nine-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 (RF) head coil. Eye data were scored off-line using ILAB software (Gitelman, 2002) and an in-house scoring suite written in MATLAB (Math Works, Inc.) running on a Dell Dimension 8300 PC. Variables of interest included correct and incorrect antisaccade latencies and error rate (number of inhibitory failures / total number of scorable trials) on rewarded and neutral trials. A correct response in the antisaccade task was one in which the subject did not look at the peripheral target when it appeared but instead looked at the mirror location. Antisaccade errors (also referred to as 'prosaccade' errors) consisted of subjects looking at the suddenly appearing peripheral stimulus. Following this initial error, nearly all subjects (>92%) corrected themselves by looking towards the appropriate (mirror) location (Velanova et al., 2008).

4.2.4 fMRI Acquisition and Preprocessing

Imaging data were collected using a 3.0 Tesla Siemens Allegra scanner at the Brain Imaging Research Center (BIRC), University of Pittsburgh, Pittsburgh, PA. A gradient-echo echo-planar imaging sequence sensitive to blood-oxygen-dependent (BOLD) contrast (T2*) was performed (Kwong et al., 1992; Ogawa et al., 1992). The acquisition parameters were: TR = 1.5 sec; TE = 25 ms; flip angle = 70 degrees; single shot; full k-space; 64 x 64 acquisition matrix with FOV = 20 x 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 x 3.125 x 4 mm voxels, which covered the entire cortex and most of the cerebellum. A three-dimensional volume magnetization prepared rapid acquisition gradient echo (MP-RAGE) pulse sequence with 192 slices (1 mm slice thickness) was used to acquire the structural images in the sagittal plane.

Functional images were preprocessed using FSL (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 (RMS) movement measures. Subjects that moved more than 1 mm (translational) or 1 degree (rotational) were excluded from additional analyses. Four adolescents were excluded based on these criteria.

Structural images (MPRAGE) were affine registered to functional images and transformed to the same dimensions using the FLIRT utility available in FSL (Jenkinson & Smith, 2001). Brain extraction was performed using the brain extraction tool (BET) in FSL (Smith, 2002). Functional images were spatially smoothed with a 5 mm Full-Width at Half Maximum (FWHM) kernel and subjected to high-pass temporal filtering (sigma = 37.5 sec) to remove low frequency scanner drift. Finally, signal intensity for each run was scaled to a mean of one-hundred and multiple runs were concatenated.

AFNI (Analysis of Functional Neuro-Images) (Cox, 1996) was used for individual subject deconvolution as well as group statistical analyses (see Group Analyses, below). Deconvolution methods followed steps delineated in Ward (1998). Briefly, our model consisted of six orthogonal regressors of interest (reward cue, neutral cue, reward preparation, neutral preparation, reward saccade response, neutral saccade response; correct antisaccade trials only), regressors for reward and neutral error trials (consisting of the entire trial), regressors for baseline, linear, and non-linear trends, as well as six motion parameters included as 'nuisance' regressors. A unique estimated impulse response function (i.e., hemodynamic response function)

for each regressor of interest (reward and neutral cue, preparation, and saccade; correct antisaccade trials only) was determined by a weighted linear sum of five sine basis functions (Johnstone, van Reekum, Urry, Kalin, & Davidson, 2007) multiplied by a data determined least squares estimated beta weight:.

$$h(t) = ß_0 * \sin \{ q * pi * (t - b)/(c-b) \} + ß_1 * \sin \{ q * pi * (t - b)/(c-b) \} + ß_2 * \sin \{ q * pi * (t - b)/(c-b) \} + ß_3 * \sin \{ q * pi * (t - b)/(c-b) \} + ß_4 * \sin \{ q * pi * (t - b)/(c-b) \}$$

Where h(t) is the estimated impulse response function at time t, ß = beta value, q = number of basis function (0-4), b = start of modeled response relative to stimulus onset (0 sec), c = end of modeled response relative to stimulus onset (18 sec). In this manner, we specified the duration of the response (18sec) for each regressor but did not make assumptions about its specific shape beyond initial amplitude of zero. Several goodness-of-fit statistics were calculated including partial F-statistics for each regressor and t-scores comparing each of the estimated beta weights to zero. Following deconvolution, statistical images were transformed into Talairach space (Talairach & Tournoux, 1988).

As a validity check for our deconvolved time courses from the separate trial epochs, we also performed the following secondary analysis. First, we summed the estimated time courses from each individual trial epoch from a single voxel, shifting the response preparation epoch time course by 1.5 seconds to account for the onset of this component in a trial and the saccade response epoch time course by 3 seconds. Next, the impulse response function for the whole trial (that is, cue, preparation, and response together) were generated by running a separate deconvolution analysis in which we coded only the start of each trial and estimated the response

up to 21 seconds after the trial onset. A comparison of the time course generated by summing the trial components (after time-shifting) and the whole-trial estimated time course from the same voxel of a single representative subject is shown as Figure 4. This analysis was repeated across subjects and brain regions and revealed no significant differences between summed and whole-trial time courses.

4.2.5 Group-level Analyses

4.2.5.1 Anatomical Regions of Interest (ROI)

Our analyses focused on functionally-defined clusters (see below) identified within the boundaries of several *a priori* anatomical regions of interest (ROI) serving putative roles in various aspects of reward processing or inhibitory/oculomotor control. Reward-related anatomical ROI in this study included the ventral striatum (including nucleus accumbens), orbitofrontal cortex, ventral medial prefrontal cortex, and dorsal medial prefrontal cortex. Given variability in the literature in terms of the nomenclature used for medial prefrontal cortical regions, we defined the boundaries of the anatomical ROI used in this study as follows. The ventral striatum (Breiter & Rosen, 1999; Breiter et al., 1997; Voorn, Vanderschuren, Groenewegen, Robbins, & Pennartz, 2004; Bjork 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. Orbitofrontal cortex (OFC) encompassed the orbital gyrus and rectus gyrus, including BA 10, 11, and 47 (Kringelbach & Rolls, 2004). Laterally, the OFC was bounded by the inferior frontal sulcus and on the medial surface by the superior rostral sulcus. Ventral medial prefrontal cortex (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, Fong, Bennett, Adams, & Hommer, 2003; Blair et al., 2006). VMPFC included rostral anterior cingulate cortex. Finally, dorsal medial prefrontal cortex (DMPFC) was bounded anteriorally by a straight line extending up (dorsally) from the AC-PC line, dorsally by the cingulate sulcus, ventrally by the callosal sulcus, and posteriorally by the precentral sulcus. DMPFC primarily included BA 24, 32 (Ridderinkhof et al., 2004; Bjork et al., 2007) and included dorsal anterior cingulate cortex. Figure 5 depicts the approximate boundaries of the medial prefrontal ROI used in this study.

Oculomotor/inhibitory control ROI included the frontal eye field (FEF), supplementary eye field (SEF), posterior parietal cortex, in particular areas in and around the intraparietal sulcus (IPS), putamen, and dorsolateral prefrontal cortex (DLPFC, including BA 9, 46) (Luna et al., 2001; Sweeney et al., 1996; Munoz et al., 2004; Pierrot-Deseilligny, Muri, Nyffeler, & Milea, 2005; Hikosaka et al., 2006; Connolly et al., 2002; Liddle, Kiehl, & Smith, 2001; Brown et al., 2006). While 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 still included primary visual cortex (V1, BA 17) as a control region to provide further evidence that in this study there were no developmental differences in the HDR function.

4.2.5.2 Time Course Analysis

Estimated impulse response values obtained from each subject's deconvolution analysis were entered into an omnibus voxel-wise 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. 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 across subjects and conditions therefore delineating the basic circuitry recruited in our study. Statistical maps (Figures 7 and 11, below) were overlaid on the anatomical image from a representative subject. For three-dimensional cortical surface images (Figures 8-10), we projected foci from Tables 2-4 showing age- and/or incentive-related effects onto 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 clusters were identified using the following methods (Velanova et al., 2008; Wheeler et al., 2005). 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 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 regions of interest were defined by including all the voxels that fell within the 9 mm sphere centered on maximum in the uncorrected image, then excluding those voxels that failed to pass corrections for multiple comparisons. In this manner, we ensured that the same regions were being considered across subjects. 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. Time courses were averaged across subjects and analyzed with repeated

measures ANOVA in SPSS; age group (adult, adolescents) 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. Of note, the feasibility of comparing BOLD time courses across developmental age groups in a common stereotaxic space has been established (Kang et al., 2003; Wenger et al., 2004; Brown et al., 2005).

4.2.6 Separate Age Group Analysis

While developmental differences are evident in the age group effects, it is informative to also examine 'main effect of time' maps for each age group separately as a means to qualitatively identify broad-stroke similarities in the pattern of brain regions engaged by each age group. For each age group, separate 'main effect of time' maps were generated for reward and neutral cue, response preparation, and saccade response epochs. These images were generated with mixed-effects ANOVA run on the estimated impulse response values from individual subjects' deconvolution analyses, with time (0 - 12 TR) as a fixed factor and subjects (n=16 for adults or n=18 for adolescents) as a random factor.

4.3 RESULTS

4.3.1 Behavior

Comparing correct response rates across age groups and incentive conditions, we observed 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 ($p=0.269$). Adolescents ($t(17)=4.500$, $p<0.001$) generated a significantly greater number of correct antisaccades on rewarded compared to neutral trials (See Figure 6A). Adults showed a trend towards more correct antisaccades on reward compared to neutral trials ($t(15)=1.939$, $p=0.072$). Adolescent correct response rates on reward trials were not statistically different from adult rates on neutral trials ($p=0.505$). 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 in inhibiting the reflexive saccade.

The latency to initiate a correct antisaccade 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 ($p>0.05$). Both adolescents ($t(17)=3.215$, $p=0.005$) and adults ($t(15)=3.498$), $p=0.003$) generated faster antisaccades on rewarded compared to neutral trials. On error trials (subjects looked at the light), repeated measures ANOVA failed to show a significant age group by incentive interaction ($F(1,23) = 2.903$, $p=0.102$). Planned within-age-group comparisons showed that adolescents generated significantly faster responses on rewarded compared to neutral trials ($t(36)=2.400$, $p=0.022$). When adults committed errors, however, the latencies did not significantly differ

across incentive type (p=0.163). Figure 6B-C plots the latencies of correct and incorrect antisaccades, respectively.

Means and standard deviations for correct response rate and latencies for correct trials are provided in Table 1.

4.3.2 Neuroimaging Results

A distributed network of brain regions was engaged during each epoch of the task in both adults and adolescents, including canonical oculomotor and inhibitory control areas (e.g., frontal and parietal eye fields, dorsolateral prefrontal cortex, and basal ganglia), as well as reward-related brain systems (e.g., VMPFC, OFC, VS) (see Figures 7 and 11). Across the three trial epochs, the pattern of activity observed changed, presumably indicating differences in the underlying processes engaged during the three epochs. These changes are examined in more detail below. Of note, only correct trials were analyzed.

4.3.2.1 Incentive Cue

Reward-Related Regions

During the presentation of the incentive cue, when the incentive is initially assessed (i.e., the subject determines whether the forthcoming trial is a rewarded or neutral trial), a significant age group by time interaction ($F(12,384)=3.082$, $p=0.023$) was observed in the time courses from right ventral striatum (14, 2, -7). This effect was due to adolescents showing an early negative response in both trial types while adults had a small early increase followed by a later, more robust positive response (Figure 8, top right). Similarly shaped time courses were observed in two regions within left VMPFC, along the left medial frontal gyrus, BA 10/ 32 (-7, 50, 8) and

more ventrally along the rostral anterior cingulate gyrus (BA 32) (-7, 41, 2) (Figure 8, middle left). Both regions showed a significant main effect of age group with adolescents showing less percent signal change than adults (left medial frontal gyrus, $F(1,32)=6.322$, $p=0.017$; anterior cingulate, $F(1,32)=6.531$, $p=0.016$).

Oculomotor and Inhibitory Control Regions

Significant main effects of age group ($F(1,32)=4.896$, $p=0.034$) and incentive condition ($F(1,32)=6.600$, $p=0.015$) were observed in a region in the left FEF (-34, -4, 35). Time courses from the left FEF (Figure 8, bottom left) showed that adults had an extended response during reward trials relative to neutral during the cue presentation that was larger than the adolescent response. Adolescents demonstrated only a weak evoked response during neutral trials in this region. A cluster in the right FEF (35, -1, 41) also demonstrated a main effect of incentive condition ($F(1,32)=4.443$, $p=0.043$). This effect was due to both age groups activating the right FEF more during reward than neutral trials, with an additional peak in adults toward the tail end of the response (Figure 8, bottom right). In the left SEF (-4, -1, 53), a main effect of age group was observed ($F(1,32)=5.034$, $p=0.032$), with adults recruiting this region more than adolescents particularly during neutral trials (Figure 8, top left). Finally, a main effect of incentive condition was also observed in the left angular gyrus (-28, -52, 38) ($F(1,32)=4.305$, $p=0.046$). This effect was primarily driven by weak evoked response in the adolescent neutral trial condition (Figure 8, middle right), similar to the left SEF response. Dorsal lateral prefrontal cortex (DLPFC) showed a main effect of time indicating that it was engaged during the task, but did not show incentive or age group effects. No significant effects were observed in the putamen during the incentive cue.

Table 2 provides the location of peak voxels and effects of all functional clusters observed in a priori ROI demonstrating significant modulation across time during the cue epoch.

4.3.2.2 Response Preparation Evoked Activity

Reward-related Regions

One functional cluster in the right ventral striatum (11, 8, -7) demonstrated significant effects of age group and incentive condition (incentive condition by age group, $F(1,32)=5.042$, $p=0.032$; time by age group, $F(12,384)=2.586$, $p=0.05$) during response preparation. Examination of the time courses from this region (Figure 9, middle left) revealed a pronounced adolescent response during reward trials but a reduced response during neutral trials. Adults demonstrated only a weak positive response during neutral trials and a later, negative-going deflection during reward trials. A similarly shaped time course profile was also observed in the right dorsal medial PFC (cingulate gyrus) BA 24, (11, 2, 44) (Figure 9, top left). This region also showed a significant incentive condition by age interaction ($F(1,32)=6.578$, $p=0.015$). No age group related effects were observed in OFC during the preparatory epoch.

Oculomotor and Inhibitory Control Regions

Extensive bilateral activity was observed in the FEF during the preparatory epoch in both groups. A region in the right FEF, BA 6 (26, -10, 44) showed a significant main effect of age group ($F(1,32)=4.598$, $p=0.040$). This effect was due to the right FEF showing greater activity in adolescents compared to adults and a higher initial peak during reward trials (Figure 9, bottom right). In the left FEF (-25, -13, 56), results indicated the following effects: age group ($F(1,32)=4.982$, $p=0.033$); incentive condition by age group ($F(1,32)=4.628$, $p=0.039$); incentive condition by age group by time ($F(12, 384)=2.889$, $p=0.032$). These effects were due to the left

FEF also showing that adolescents had a higher early peak relative to adults across both incentive types, as well as a temporally extended response during reward trials (Figure 9, bottom left). Similar to the left FEF, a cluster in the right SEF (5, 2, 56) also demonstrated a main effect of age group ($F(1,32)=4.892$, $p=0.034$) and had time courses showing higher activity for adolescents compared to adults and an extended response during reward trials (Figure 9, top right).

In posterior parietal cortex, a cluster in right precuneus (BA 7) (8, -58, 53) showed a main effect of age group ($F(1,32)=7.441$, $p=0.010$) and a time by age group interaction ($F(12,384)=3.093$, $p=0.024$). As demonstrated by the time courses from the right precuneus cluster (Figure 9, middle right), adolescents compared to adults had greater evoked activity in this region for both incentive trial types. No age group or incentive-related effects were observed in putamen or DLPFC; however, regions in middle and inferior frontal gyri demonstrated significant main effects of time (all p's < 0.01) (Table 3).

Table 3 provides the location of peak voxels and effects of all functional clusters observed in a priori ROI demonstrating significant modulation across time during the response preparation epoch.

4.3.2.3 Saccade Response Evoked Activity

Reward-related Regions

One cluster in left rectal prefrontal gyrus/medial OFC (BA 11/10) (-7, 38, -13) showed a significant main effect of age group ($F(1,32)=4.752$, $p=0.037$). Time courses from this cluster showed a greater negative-going response in adolescents compared to adults that was temporally extended for reward trials (Figure 10, bottom). Significant effects were also observed in the left cingulate gyrus/dorsal medial PFC, BA 24 (-1, 11, 35) (incentive condition by age group,

F(1,32)=4.990, p=0.042; incentive condition by age group by time, F(12, 384)=2.860, p=0.037). Time courses from this region (Figure 10, top) showed a similar initial peak in adults during reward trials and in adolescents during neutral trials. However, adolescents showed a later negative-going response during reward trials. No significant activation was observed in the ventral striatum during the saccade response epoch.

Oculomotor and Inhibitory Control Regions

Extensive activity was observed in the *a priori* oculomotor control regions in both age groups during the saccade response epoch, including FEF, PPC, and putamen. However, none of these regions showed significant effects of age or incentive type.

Table 4 provides the location of peak voxels and effects of all functional clusters observed in a priori ROI demonstrating significant modulation across time during the saccade response epoch.

4.3.2.4 Control Region: Primary Visual Cortex

Functionally defined clusters in primary visual cortex during each trial epoch were examined as a control given that this area demonstrated robust participation in the antisaccade task. As expected, no age group or incentive-related effects were observed in primary visual cortex during any trial epoch (all p's > 0.05) and the hemodynamic response was well-defined in both age groups (Figure 12).

4.3.2.5 Age Group Results

Adolescents compared to adults showed a later recruitment of reward-related circuitry, particularly the ventral striatum (Figure 8 and 11A). During reward trial cue presentation, adults showed significant modulation in bilateral ventral striatum and a region in ventromedial prefrontal cortex that extended ventrally into medial OFC (BA 11). Adolescents, in contrast, did not significantly recruit the ventral striatum until the response preparation epoch and did not show significant modulation of VMPFC or medial OFC during any trial epoch at the individual age group level (Figure 11B). During neutral trials, neither age group showed significant modulation in ventral striatum. However, adults recruited VMPFC (BA 10, 32) during the cue of neutral trials. This region was distinct from that observed during the reward cue in that it was more dorsal and extended rostrally into BA 10. Adults and adolescents were highly similar in terms of oculomotor control regions recruited during the saccade response epoch; this was particularly evident during reward trials (Figure 11C).

4.4 DISCUSSION

We examined reward processing and effects on response inhibition at different temporal stages in healthy adults and adolescents using a novel, incentive-mediated antisaccade paradigm. Behaviorally, adults and adolescents demonstrated significantly enhanced performance during rewarded relative to neutral trials. Distinct neural mechanisms were found to underlie these behavioral improvements in the adult and adolescent systems, however. Notably, adolescents demonstrated evoked signal changes in specific reward related circuitry (e.g., ventral striatum)

and oculomotor control regions (e.g., FEF) during a later component of reward trials compared to adults. These effects are discussed in more detail below.

4.4.1 Reward Contingency Affects Inhibitory Control

Behaviorally, adults and adolescents demonstrated fewer inhibitory failures and faster correct antisaccades on rewarded compared to neutral antisaccade trials reflecting motivational effects of reward processing. This effect was significantly greater for adolescents. Additionally, both age groups generated faster incorrect antisaccades on rewarded compared to neutral trials. These results are consistent with previous behavioral work showing enhanced antisaccade performance with reward (Jazbec et al., 2006; Duka et al., 1997; Hardin, Schroth, Pine, & Ernst, 2007; Jazbec et al., 2005). Our results indicate that monetary incentives influence response inhibition, a basic component of cognitive control, and that essential components of the circuitry supporting this modulation are on-line by adolescence.

We also observed developmental differences in how rewards impact error trial latencies, with adolescents but not adults generating faster prosaccade errors on reward compared to neutral trials indicating a speed-accuracy trade-off. In non-human primates, rewards have been shown to facilitate motor performance (i.e., motivation) by modulating neuronal activity levels (Hikosaka et al., 2006). In adolescents, reward contingency may heighten overall activity levels in the immature inhibitory system, already engaged to a high degree to achieve adult-like behavioral output (Luna et al., 2001), and thus may expose vulnerabilities to error. The result may be more frequent and faster errors; in short, a more impulsive system.

4.4.2 Developmental Differences in Reward Processing

While both adult and adolescent behavioral performance was enhanced on rewarded trials, we observed developmental differences in terms of when during a trial reward circuitry was recruited, as well as when enhanced activity in inhibitory control circuitry was noted. This suggests that different components of reward-processing circuitry and, importantly, the functions that they subserve, may have distinct developmental trajectories. Importantly, these results also inform a debate in the literature concerning hypo- versus hyper-reactivity of the adolescent reward system, discussed below.

The ventral striatum (VS) has been consistently implicated in the anticipatory processing of rewards, including reward detection and prediction (Knutson et al., 2005). Consistent with these roles, we found that adults showed early recruitment of VS during the initial presentation of the reward cue. However, this region was not significantly engaged in adults during the response preparation epoch. These results indicate that the mature VS primarily supports initial aspects of reward assessment and anticipatory processing in the antisaccade task, possibly alerting other brain processes when future behavior may be associated with rewards. In contrast, adolescents failed to show this early recruitment of VS. This is consistent with adolescent hypo-responsiveness during anticipatory processing (Bjork et al., 2004), which has been argued as indicating an under-active reward system. Instead, adolescents showed a later recruitment of VS during the response preparation period which reached a greater peak magnitude relative to the adult cue-related response (adult percent signal change reached 0.1% compared to the adolescent peak of 0.4%, see Figures 8 and 9) as found in other studies (Ernst et al., 2005). This characterization of the VS as 'sluggish' with a delayed but over-active response may help reconcile contrasting models of immature VS responding in the literature indicating both hypo-

and hyper-activity of ventral striatum in the adolescent system (Spear, 2000; Ernst et al., 2006; Chambers et al., 2003). One potential implication of these results may be that adolescents are slower to initially recognize reward contingencies and to generate representations of predicted rewards during decision-making, particularly under conditions requiring relatively fast responses. Once the reward system is engaged (e.g., after a delay or in response to a particularly salient stimulus), however, adolescents may have heightened sensitivity to rewarding stimuli, suggesting that acquiring rewards may play a more prominent role and perhaps bias their decision-making. Alternatively, adolescents may show limitations in initially assessing reward contingencies but have increased reactivity to response anticipation.

VMPFC has been implicated in processing related to reward expectation and value-based decision-making (Blair et al., 2006; Daw, O'Doherty, Dayan, Seymour, & Dolan, 2006; Keedwell, Andrew, Williams, Brammer, & Phillips, 2005; Gläscher, Hampton, & O'Doherty, 2008). Similar to VS, we found that adults recruited regions of VMPFC during the presentation of both reward and neutral cues (see Figure 11B). Individual age group analysis revealed that during reward trials, this VMPFC activation coalesced with activation in medial OFC (BA 11). However, during neutral trials the activation seen in VMPFC extended rostrally into BA 10. These results suggest that the VMPFC may function cooperatively with medial OFC in forming early representations of the value associated with a reward-predicting stimulus in the mature system. Adolescents were found to under-activate specific regions of the VMPFC compared to adults. Thus, adolescents may be limited in their ability to integrate predicted or expected rewards into on-going behavior and decision-making. An intriguing, albeit speculative, extension of these results is that adolescents may operate in a more explorative versus exploitive behavioral

mode during value-based decision-making due to their hypo-functioning VMPFC (Daw et al., 2006).

OFC has been implicated in numerous aspects of reward processing (Kringelbach et al., 2004), including coding representations of incentive valence (O'Doherty et al., 2001) and subjective value suggesting an executive assessment of rewards (Hare et al., 2008). Both age groups recruited lateral OFC during the cue, indicating that some aspects of OFC functionality, which may include updating value representations associated with the cue based on performance (Breiter et al., 2001; Roesch et al., 2004; Elliott et al., 2003; O'Doherty et al., 2001), are established by adolescence. We also found age-related effects in medial OFC during the saccadic response of rewarded trials possibly reflecting developmental differences in feedback processing. While subjects were not given extrinsic feedback in this task based on their performance, they did demonstrate evidence for intrinsic feedback when a mistake was made. Subjects invariantly followed incorrect antisaccades with corrective saccades toward the appropriate location, consistent with previous reports (Velanova et al., 2008). In adolescents and adults, the magnitude of signal changes in this region was larger for rewarded trials than neutral trials. However, in adolescents, activity was more negative-going on rewarded trials relative to neutral, while in adults the response to reward trials was more positive. Negative time courses have been proposed to reflect decreased neuronal activity (Gusnard & Raichle, 2001), thus, these data suggest that adolescents may be limited in specific aspects of evaluative reward processing.

One proposed role of the dorsal medial prefrontal cortex is the integration of monetary rewards with motor responses (Williams, Bush, Rauch, Cosgrove, & Eskandar, 2004). During the response preparation epoch of reward trials, we found that adolescents recruited the DMPFC to a much greater extent than adults. This result suggests that the DMPFC may be recruited more

extensively during adolescence in order to relate reward information to areas involved in oculomotor control (FEF, SEF). Another suggested role of DMPFC is in monitoring behavioral outcome (Ridderinkhof et al., 2004). We found that adolescents showed differential responses relative to adults in DMPFC during the saccade response epoch consistent with outcome processing. As mentioned above, while this study did not have explicit feedback during the saccade response epoch, all subjects corrected themselves after prosaccade errors indicating that they were aware of errors. Taking this into consideration, our time course results (Figure 10) preliminarily suggest that adolescents may process trial outcomes differently than adults, perhaps viewing neutral (non-gain) trials as more punishing. Future work focused on activation evoked by explicit error feedback could clarify this issue.

Moreover, as expected, we found recruitment in regions consistently implicated in inhibitory and oculomotor control, including the cortical eye fields (Luna et al., 2001; Brown et al., 2004; Munoz et al., 2004; Everling, Dorris, & Munoz, 1998). We found that activity in specific foci within these anatomical regions (see Figures 8 and 9) was enhanced during rewarded trials, indicating that activity in regions known to support antisaccade performance are indeed influenced by reward contingency. Critically, the modulation of oculomotor and inhibitory control circuitry occurred in parallel with the peak of reward system activity in each age group - earlier during the cue for adults (Figure 8) and later during response preparation for adolescents (Figure 9). Adolescents showed an even larger recruitment of these regions, perhaps reflecting the higher demand on their ability to perform the task and the recognition by the reward system that these regions are needed to perform correct trials.

4.4.3 Conclusions

In sum, results suggest that reward contingency affects inhibitory control in both adults and adolescents, presumably by modulating activity in task-necessary oculomotor control regions like FEF and SEF. Developmentally, our results suggest that adults recruit the VS and VMPFC earlier in a trial than adolescents, during the incentive cue (reward assessment), while adolescents recruited VS later and to a greater extent during response preparation (reward anticipation). This result points to persistent immaturities in the adolescent reward system, reflecting both under- *and* over-activity. Taken together, our results suggest that adolescents may have immaturities in the ability to promptly access reward circuitry compared to adults when making decisions with reward contingencies, which, in concert with inconsistencies in inhibitory control, could contribute to sub-optimal choice behavior and vulnerability to risk taking.

5.0 STUDY 2: REWARD MAGNITUDE MANIPULATIONS DIFFERENTIALLY AFFECT BEHAVIORAL PERFORMANCE IN ADOLESCENTS COMPARED TO ADULTS

5.1 INTRODUCTION

Voluntary response suppression, or response inhibition, refers to the ability to halt a prepotent or reflexive response in favor of goal-appropriate action (Luna et al., 2004a). Previous work from our laboratory and others using the antisaccade (AS) task (Hallett, 1978), which measures the ability to halt a saccade to a suddenly appearing peripheral stimulus, have repeatedly shown that behaviorally adult-like levels of response suppression are reached in mid-adolescence or later (Fischer et al., 1997; Fukushima et al., 2000; Klein et al., 2001; Luna et al., 2004a; Munoz et al., 1998). However, the neural circuitry supporting AS task performance undergoes continued refinement through adolescence (Luna et al., 2001). These data support other work using alternative paradigms (e.g., Go/No-go, Stop-Signal tasks) indicating a protracted maturation of inhibitory control (Levin et al., 1991; Williams et al., 1999; Liston et al., 2006; Ridderinkhof et al., 1999; Paus et al., 1990; Luciana et al., 1998; Tipper et al., 1989; Ridderinkhof et al., 1997).

Less is known about how other functional systems, like reward processing, affect performance on response inhibition tasks in adolescents. Understanding this interaction in a normative population may provide insight on basic mechanisms underlying the emergence of

risk taking, a serious health concern for this age group (Arnett, 1992; Steinberg, 2004; Dahl, 2004). Two recent developmental studies have empirically examined this interaction behaviorally by adding trial-by-trial reward contingencies to a typical AS task (Jazbec et al., 2006; Hardin et al., 2007). Both of these studies report that rewards similarly decrease the number of errors generated by adolescents and adults, in line with similar adult studies (Blaukopf et al., 2006; Duka et al., 1997). The effects of rewards on antisaccade latencies appear to be more variable, however. Jazbec et al. (2006) found that the latencies of directional (prosaccade) errors and peak velocities of correct antisaccades are differentially affected in adolescents compared to adults, but found null effects on correct antisaccade latencies (Jazbec et al., 2006). In contrast, Hardin et al. (2007) found that rewards aligned adolescent correct antisaccade latencies with those of adults. Interestingly, larger magnitude incentives were not found to exert a greater influence on behavior across the age groups in this study (Hardin et al., 2007). However, data from the broader developmental (Galvan et al., 2006) and adult reward literatures (Delgado et al., 2003) have typically shown concomitant performance gains with increased incentive magnitudes.

While significant advances have been made in these initial studies, our understanding of reward influences on response inhibition in adolescence remains limited. For example, while Hardin et al. (2007) utilized different magnitudes of rewards and losses, only three levels of reward salience were used (high, medium, and low). A wider range of possible magnitudes could better characterize the nature of reward-induced changes in saccade parameters. Furthermore, in each of the studies described above, money was used as the incentive for adolescents and adults. A powerful motivator, money is frequently used in the human reward literature given that it holds significant value to (most) participants and the magnitude is easily quantified, represented,

and manipulated. However, the use of money (or any incentive that is fixed across subjects or age groups) also introduces complexities that have not yet been fully explored. For example, it may be the case that different age groups vary in terms of how valuable they deem a set dollar amount (e.g., based on past experience, employment, current financial status, etc.). This notion is succinctly summarized in the question: *"Does a dollar mean the same thing to a teenager as it does to an adult?"* Given that motivation to engage in a certain behavior depends, in large part, on the anticipated value of the associated incentive (Roesch et al., 2004), some portion of the observed performance differences in adolescents compared to adults on the rewarded AS tasks reported above may have resulted from age-related differences in monetary incentive valuation and motivation. Interestingly, several recent studies have identified individual differences in reward-related brain responses (Spreckelmeyer et al., 2009; Bediou, Eimer, d'Amato, Hauk, & Calder, 2009; Koeneke, Pedroni, Dieckmann, Bosch, & Jancke, 2008), yet to our knowledge no study to date has examined differential responses to the value of money across different subjects or age groups.

In this study, we tested healthy adolescents and adults using an incentive-mediated antisaccade task designed to more fully characterize the effects of different reward and punishment magnitudes on antisaccade performance, while also implementing simple measures aimed at *minimizing* potential differences in the incentive value of the promised reward. It should be noted that the 'value' of an incentive is a complex, multi-dimensional construct (see Chapter 2), so we stress that our methods aimed to *minimize* age group differences on specific dimensions rather than *equate* value, per se. Toward this end, we did the following. First, each subject had the opportunity to choose the reward for which he or she would be working (i.e., maximize subjective preference). Prior to testing, subjects chose to work for either a pre-paid debit card or

one of several gift cards to various stores or restaurants (see Methods), whichever the participant deemed to have the highest subjective appeal. Second, subjects could either immediately gain (reward trials) or lose (punishment trials) 1 to 5 arbitrary 'points' depending on their performance rather than winning or losing actual dollar amounts, *per se*. The number of points at stake on each trial was indicated by the number of green bars above (reward) or red bars below (punishment) a central fixation (Figure 13). Finally, in this experiment we established a set range of points that could be earned towards the reward. In this manner, both adolescents and adults were operating in the same 'fixed-economy', which meant that the incremental worth of a point available on each valenced trial relative to the total was constant across age groups.

We hypothesized that higher reward magnitudes (trials with more points at stake) would enhance adolescent task performance to a greater extent than adult, evident by a reduced error rate. We based this hypothesis on the notion that adolescents may have an initially sluggish reward system that becomes more engaged, relative to adults, with larger (and more salient) rewards and that this heightened reactivity would positively enhance performance, as indicated in our previous work (study 1) and by others (Ernst et al., 2005). In particular, we sought to determine whether this increase in gains on larger magnitude rewards would align adolescent performance to that of adults. Further, we hypothesized that adults would perform better (lower error rates) on punishment trials relative to adolescents, in part due to more mature brain systems mediating risk-assessment (Ridderinkhof et al., 2004; Bjork et al., 2007; Eshel et al., 2007; van Leijenhorst et al., 2006; Galvan et al., 2006).

5.2 METHODS

5.2.1 Participants

Thirty-one adolescents (13-17 years, M = 15.39 (SD = 1.36), 16 females) and thirty-four adults (18-26 years, M = 21.56 (SD = 2.38), 16 females) participated in this study. All subjects had far visual acuity of at least 20/40 (corrected or uncorrected) and medical histories that revealed no neurological disease, brain injury, and no history of personal or first degree relative major psychiatric illness (determined by interview). Age ranges for each group were selected based on previous work indicating differential behavioral performance levels on the antisaccade task (Luna et al., 2004a). Participants and/or their legal guardians provided informed consent or assent prior to participating in this study. All experimental procedures in 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 in addition to performance-related earnings.

5.2.2 Minimizing Incentive Value across Age Groups

Several methods were implemented to minimize possible differences in reward value across the age groups. First, prior to eye tracking, each subject completed a brief questionnaire asking him or her to choose one of several potential rewards that they would be working towards. Reward options included either a pre-paid debit card or a $25.00 gift card redeemable at various restaurants and businesses. (Note: determination of which gift cards were offered, which included iTunes, Home Depot, McDonald's, among others, was based on informal interviews

with adolescents and young adults, asking them what gift cards they would find rewarding). The debit or gift card was offered in addition to the subject participation payment, which was received regardless of performance. In this manner, each participant chose a reward with the highest subjective preference, which is one primary component of value (see Chapter 2). Each subject was also asked to rate how valuable (7-point Likert scale) they considered their chosen card to be and to write down at least one item that they might purchase with it as a means to increase the motivational salience of the card. Subjects were instructed that they could potentially win (rewarded trials) or lose (potential loss or 'punishment' trials) points throughout the experiment depending on their performance and that these points would be tallied at the end of the session to determine their reward. Subjects were told that they would begin with 100 points to provide initial motivation and assured that no debt could be accrued. Subjects were remunerated based on the proportion of points earned out of a total of 220 possible using the following scale:

Points Earned	Amount earned
≤140	$5.00
141 to 160	$10.00
161 to 180	$15.00
181 to 200	$20.00
≥201	$25.00 or subject-selected gift card

5.2.3 'Bars' Antisaccade Task

Subjects were first presented with one of eleven incentive cues (1.5 sec) displayed at beginning of each antisaccade trial (Figure 13). Green filled bars (1, 2, 3, 4, or 5 bars) above a central white fixation indicated that they could win points if they correctly performed the trial (potential reward trial). Incorrect performance on reward trials did not result in point loss. Red filled bars (1-5) below the white fixation indicated they would lose points if they generated an error

(potential loss or punishment[2] trial). Correct performance on punishment trials did not result in point gain. In order to minimize the engagement of working memory systems, subjects were instructed that the computer would keep score and that they should not keep a running tally of their points as this could negatively impact their performance. Empty bars above and below the fixation indicated that no points were at stake and that the subject's total points would remain the same regardless of performance (neutral trial). Next, the incentive cue image disappeared and the central fixation cross changed from white to red (1.5 sec). Subjects were told before the task that they should begin to prepare a response during this time. Finally, a peripheral stimulus (yellow dot subtending approximately 0.5 degrees/visual angle) appeared at an unpredictable horizontal location (approximately ± 4 and 8 degrees/visual angle) (1.5 sec). Subjects were instructed not to look at the stimulus when it appeared but instead direct their eyes to the mirror location. Antisaccade errors (also referred to as 'prosaccade errors') consisted of saccades made toward the peripheral target. During the saccade response epoch, eye movement data were scored on-line using an in-line E-Prime script. Briefly, this script detected if at anytime during the first 1000msec of the response epoch the subject generated an eye movement toward the peripheral target, or if no eye movement was generated. If so, an auditory tone (1163Hz peak frequency; 'D') was played for 400msec to indicate an incorrect response. If instead the subject initially looked toward the mirror location of the target during this 1000msec window, a correct response,

[2] The use of the term 'punishment' here refers to trials where points may be taken away if an antisaccade error is committed. This definition is different from the more technical usage in operant conditioning studies, in which punishment is related to the reduction of a certain behavior by either removing or applying a stimulus.

a 400msec sound of a cash register ('cha-ching') was played (1516Hz peak frequency, 'F-sharp'). Auditory tones were modified using Audacity, an open-source sound editing program (http://audacity.sourceforge.net). Finally, between all trials a white fixation cross appeared in the center of the screen (1.5 sec). Sixty trials (20 reward, 20 potential loss, and 20 neutral trials) were presented during each run, for a total run time of 6 minutes. Two runs were presented per experimental session.

At the end of the experimental session, subjects completed a second questionnaire asking them to rate (7-point Likert scale) how valuable they deemed their chosen reward, how they felt after viewing the reward and punishment cues, how they felt after hearing the feedback sound(s), how many points and how much money they thought they earned, and if they felt that the incentives affected their performance. Standard indices of socio-economic status (SES; maternal and paternal education level, income) were also collected for each subject.

5.2.4 Eye Tracking

Subjects were seated in a darkened room with their head comfortably positioned on a chin rest with a Velcro head restraint. Eye movements were obtained using a near-infrared table-mounted eye-tracking system (Model 504; Applied Science Laboratories, Bedford, MA, USA) that recorded eye position by pupil and corneal reflection. At the beginning of each eye-tracking session and between runs when necessary, a nine-point calibration procedure was performed. Stimuli were presented using E-Prime (Psychology Software Tools, Inc., Pittsburgh, PA) displayed on a PC monitor positioned 56cm directly in front of the subject.

In addition to the on-line scoring used for auditory feedback (which was limited to 'correct' or 'incorrect'), eye tracking data were scored off-line for various saccade-related

parameters, including latency (correct and incorrect saccades) and prosaccade error rates using ILAB software (Gitelman, 2002) and an in-house scoring suite written in MATLAB (Math Works, Inc.) running on a Dell Dimension 8300 PC. Saccades were identified using a velocity algorithm in ILAB employing a 30 degrees/sec criterion. Eye recordings were reviewed and modifications were made when necessary using the editing features available in ILAB. Our primary eye movement measurements have high reliability (ICC > 0.90).

5.2.5 Statistical Analyses

To investigate the effects of age group, valence, and magnitude, as well as their interaction on error rates and latencies of correct antisaccades, we ran an omnibus repeated-measures ANOVA, with magnitude (1-5) and valence (reward, punishment) as the within subjects factors and age-group (adults, adolescents) as the between subjects factor. Neutral trials were not included in this model given that these trials did not vary in magnitude. The latencies of prosaccade errors were also not examined in this model due to insufficient data, a result of few errors being made in this task. Mean prosaccade error rates and latencies of valenced trials (collapsed across magnitudes) were compared with neutral trials values across age groups using independent samples t-tests and within each age group using paired samples t-tests.

Given our prediction that adolescents and adults would be differentially affected by incentive magnitude manipulations, separate repeated measures ANOVA were also run on reward and punishment trials for each age group, with incentive magnitude as the within subject factor. In this manner, simple effects of magnitude unique to each age group and valence could be assessed. Paired t-tests were used to compare the effects of different magnitudes of incentives within each age group.

Finally, while we expected that incentive effects would be observed at the age group level, the influence of incentives on behavioral performance likely varies *within* each age group as well (i.e., subject level). To gain leverage on how many subjects in each age group were sensitive to the effect of incentives on performance relative to the neutral condition, non-parametric Wilcoxon Signed Ranks tests were performed for reward vs. neutral and punishment vs. neutral trial error rates and correct antisaccade latencies.

5.3 RESULTS

5.3.1 Participants

As determined by the Wechsler Abbreviated Scale of Intelligence (WASI; 2-part), IQ's for both adults and adolescents were in the normal range (adults, M=119.73, SD=10.61; adolescents, M=107.20, SD=11.23). Adults and adolescents did not differ on various socio-economic indices including maternal education ($t(56)=0.973$, $p=0.335$), paternal education ($t(56)=0.720$, $p=0.475$), maternal income ($t(56)=0.962$, $p=0.340$), or paternal income ($t(56)=0.492$, $p=0.624$).

Mean adolescent estimated earnings were 150.77 (SD= 69.36) points and $22.00 (SD=6.56). Mean adults estimated earnings were 158.94 (SD= 61.01) points and the full $25.00 (SD=15.8). Adolescents actually earned M= 196.16 (SD = 33.22) points and M= $21.2 (SD = 6.96) dollars, while adults earned M= 203.04 (SD = 15.41) points and M= $23.15 (SD = 2.82) dollars. Although most participants chose the pre-paid debit card as a reward, 8 of 34 adults and 5 out of 31 adolescents selected an alternative gift card suggesting some variability in what subjects find rewarding. Importantly, adolescents and adults did not differ in terms of their

ratings of how valuable they found there chosen reward (Adults, M = 2.00 (SD = 1.44); Adolescents, M = 2.63 (SD = 1.67); 7-point scale with 1= extremely valuable and 7 = not very valuable; p=0.11). Interestingly, adolescents rated feeling slightly more positive (7-point scale, 1= very negative and 7 = very positive) after first seeing the green reward bars (M = 5.90, SD = 1.04) than did adults (M= 5.36, SD = 1.22), but this difference also failed to reach significance (t(62)=1.895. p=0.063).

5.3.2 Bars Antisaccade Task

5.3.2.1 Error Rate

ANOVA revealed a significant main effect of age group on error rate during reward trials, F(1,63)=4.303, p=0.042). This effect was driven by adolescents generating overall more errors (7.4 +/- 1.3%) than adults (3.6 +/- 1.3%), t(63)=2.074, p=0.042. A significant main effect of valence on error rate was also observed (F1, 63)=6.267, p=0.015). Collapsed across age groups, mean error rates were higher on reward trials (6.6 +/- 1.2%) compared to punishment trials (4.3 +/- 0.8%), t(63)=2.403, p=0.019 (see Figure 14). Adolescents generated fewer errors on punishment trials compared to neutral trials (t(30)=2.060, p=0.048), but did not differ in terms of reward and neutral trial error rates (t(30) = 1.192, p=0.243). Adult error rates did not differ across different valences.

Considering reward trials separately, collapsed across magnitude, a significant main effect of age group was observed, F(1,63)=4.754, p=0.033. This effect was driven by adolescents generating overall more errors than adults, t(63)=2.180, p=0.033 (Figure 14, left cluster of bars). When examining error rates at each reward magnitude, adolescents had significantly higher error rates on 2-bar trials compared to adults, (t(63)=2.262, p=0.027 (Figure 15). Considering

adolescents alone, we observed a significant improvement in performance (i.e., decreased prosaccade error rate) with increased reward magnitude. Planned pair-wise t-tests of reward magnitudes showed that adolescents generated fewer errors on higher magnitude trials (mean error rate on 4 and 5 point trials) compared to low magnitude trials (mean error rate on 1 and 2 point trials) ($t(30)=2.377$, $p=0.024$) (Figure 15). In contrast, adults did not show similar performance improvements across reward magnitudes.

On punishment trials, collapsed across magnitude, adolescents and adults did not differ in terms of prosaccade error rates (p's >0.05) (Figure 14, middle cluster of bars). When examining error rates at each punishment magnitude however, adolescents generated significantly more errors on punish 3-bar trials compared to adults, $t(63) = 2.293$, $p = 0.025$ (Figure 16).

5.3.2.2 Latencies of Correct Antisaccades

No significant main effects of age group, valence, or magnitude, or any interactions were observed for latencies of correct antisaccades using ANOVA. Figure 17 shows the latencies of correct antisaccades across reward and punishment magnitudes for each age group.

5.3.2.3 Latencies of Prosaccade Errors

In all cases, as expected from the literature (Munoz et al., 2004), the latencies of prosaccade errors were significantly lower (i.e., faster) compared to correct antisaccades for adult reward ($t(12)=4.087$, $p=0.002$), punishment ($t(14)=3.751$,$p=0.002$), and neutral ($t(15)=3.928$, $p=0.001$) trials, as well as adolescent reward ($t(22)=2.378$, $p=0.027$), punishment ($t(17)=6.454$, $p<0.001$), and neutral ($t(23)=4.731$, $p<0.001$) trials (Figure 18C). Comparing across age groups and valence, adults and adolescents did not significantly differ in the latencies of prosaccade errors.

Figure 18A-C shows the latencies of errors across reward and punishment magnitudes for each age group, as well as plots mean latencies of correct and incorrect responses for comparison.

5.3.2.4 Responsiveness to Incentives: Non-parametric tests

To gain leverage on how much of an effect the reward or punishment contingency had on each individual subject's performance, we plotted performance (error rate and latency) on neutral trials and on valenced (reward, punishment) trials for each adolescent and adult (Figure 19-20). In these plots, data points below the diagonal line (defined by y = x) indicate higher values for neutral trials while points above the line indicated higher values for reward or punishment trials. Thus, for the error rate plots (Figure 19), subjects who performed better (made fewer errors) on trials with a reward or punishment contingency compared to neutral are below the diagonal line. For the latency plots (Figure 20), subjects who generated faster correct antisaccades (lower latencies) on trials with a reward or punishment contingency are also below the diagonal line. Significant results as determined by Wilcoxon Signed Rank tests are described below. Though not plotted, we also examined effects at each reward and punishment magnitude (1 through 5) and report significant differences below.

For adolescents, 17 out of 31 individuals (54.8%) showed a higher error rate for neutral relative to punishment trials (collapsed across magnitudes) ($Z = -2.144$, $p=0.032$, Wilcoxon test). On 4-point reward trials, 20 of 31 adolescents (64.5%) showed a higher error rate for neutral trials ($Z = -2.106$, $p=0.035$, Wilcoxon test). On 3-point punishment trials, 19 of 31 adolescents (61.3%) had higher error rates on neutral trials ($Z = -2.070$, $p=0.038$). In terms of correct antisaccade latencies, on 5-point reward trials, 21 of 31 adolescents (67.7%) showed a higher latency for neutral trials ($Z=-2.038$, $p=0.042$, Wilcoxon test).

For adults, 25 out of 34 individuals (73.5%) showed a higher latency (slower response time) for reward trials relative to neutral trials ($Z = -1.992$, $p=0.046$, Wilcoxon test). In terms of error rates, on 3-point punishment trials, 17 out of 34 adults (50.0%) showed a higher error rate for neutral trials ($Z = -3.473$, $p=0.001$, Wilcoxon test).

5.4 DISCUSSION

We examined the effects of different magnitudes of reward and punishment on response inhibition in healthy adults and adolescents using a novel, incentive-mediated antisaccade paradigm with auditory, performance-based feedback. In addition, we implemented several pre-test measures intended to minimize potential differences across age groups in terms of the value of the reward for which they were working. Notably, we found evidence for differential effects of reward magnitude on antisaccade performance in adolescents but not adults. Our results are discussed in more detail below.

5.4.1 Adolescent Error Rates are Sensitive to Reward Magnitude

Changes in reward magnitudes differentially affected error rates in the adolescent group (Figure 15). On low magnitude reward trials (1-2 points), adolescents were generating errors approximately 12% of the time. However, on higher magnitude trials, adolescent error rates greatly improved, falling to approximately 6%. In fact, adolescent error rates were aligned with adults on rewarded trials with higher magnitudes (4-5 points). In contrast, changes in reward magnitudes did not significantly improve adult error rates. One interpretation of this null effect

in adults is that they were simply not motivated by or sensitive to the rewards offered in this study. Three lines of evidence argue against this conclusion, however. First, non-parametric tests showed that 25 of 34 adults (73.5%) demonstrated longer latencies for correct antisaccades on reward trials compared to neutral. This result suggests that adult performances during reward trials resulted in longer planning and that they were sensitive to reward contingency. Furthermore, although the task parameters were not identical, adults in this study performed considerably better on the rewarded AS task compared to previous reports using a non-incentive AS task, on which error rates are typically in range of 15-30% (Luna et al., 2004a; Luna et al., 2001; Velanova et al., 2008). This observation also supports the notion that adult performances were sensitive to rewards in this experiment. Finally, adults and adolescents did not differ in terms of how valuable they subjectively rated their chosen reward. An alternative explanation for the low error rates observed in the adult group is that they were motivated to do well on the task regardless of how many points were available to be earned, resulting in a ceiling effect. Adolescents, on the other hand, appeared to be more engaged during reward trials with more points on the line (e.g., higher salience) and given their overall poorer performance were able to show improvements (no ceiling effect). An immature adolescent reward system more sensitive to relatively high immediate gains (study 1) would be consistent with the observed behavior.

On punishment trials, both adolescents and adults performed consistently well, with each age group generating less than 8% errors across the magnitude levels (Figure 16). These results suggest that both age groups consistently tried to minimize potential losses, even minor ones. The fact that adolescents performed at adult-like levels even on the lowest magnitude (1-point) punishment trials could reflect a common observation in the decision-making literature that losses tend to be weighted more heavily than gains, generally by a 2:1 gain to loss ratio (Tversky

& Kahneman, 1981). Our results suggest that this gain to loss ratio may be similar for adolescents and adults. It should be noted, however, that there are limitations equating reward and punishment and that this task may be biased towards punishment.

On neutral trials, adolescents performed significantly worse than adults, generating errors at a rate approximately twice that of adults (Figure 14). These data suggest that on trials where no points are at stake, adolescents are not getting the same motivational 'boost' in performance from reward-related circuitry as on incentive trials and were instead reliant on their relatively immature cognitive control abilities. The low error rates observed in adults even during neutral trials may represent a carry-over effect from reward and punishment trials, resulting from adults trying to maximize their performance across all trials.

The latencies of correct antisaccades were not statistically different across the age groups for any incentive trial type. We interpret this observation as follows. Correct performance on the antisaccade task first requires the suppression of the prepotent tendency to saccade towards the visual stimulus, followed by a volitional eye movement to the mirror location (Munoz et al., 2004). Our data suggests that incentives may be more strongly affecting brain regions key to the ability to suppress the reflexive saccade to the peripheral stimulus, which occurs at the time of the response and would impact error rates, and exerts less of an influence on brain systems underlying the secondary, volitional saccade generated to the mirror location, which relies on response preparation and affects latencies.

5.4.2 Possible Mechanisms of Rewarded Eye Movements

Although the neural mechanisms underlying enhanced AS performance on incentive trials has not yet been fully characterized in humans, pathways involved in rewarded eye movements have

been identified in the non-human primate literature. In fact, the influence of incentives on brain areas key to saccade generation has been well-characterized at the single unit level in non-human primates (Hikosaka et al., 2000; Amador, Schlag-Rey, & Schlag, 2000; Kawagoe, Takikawa, & Hikosaka, 1998). For example, Hikosaka and colleagues (2000) demonstrated in monkeys that memory-guided saccades to a previously rewarded location had lower latencies and higher peak velocities compared to saccades made towards non-rewarded locations. These effects stemmed from a pre-saccade buildup of activity in contralateral caudate motor (saccade-generating) neurons via projections from midbrain dopaminergic neurons activated by expected rewards (for complete review of circuitry, see Hikosaka et al., 2000).

Enhanced performance on rewarded antisaccade trials may be affected by increased sub-cortical, dopaminergic inputs (via the basal ganglia) affecting superior colliculus (SC) saccade-generating 'burst' neurons (Leigh et al., 1999). Future work will be needed to determine whether input from the basal ganglia directly inhibit the SC saccade motor neurons or enhance fixation neurons in SC (which reciprocally inhibit saccade generating neurons), or both, during task performance. Further, the delineation of top-down influences on SC from fixation neurons in FEF, as well as input from SEF, will also be critical. Importantly, distinct reward-predicting and reward-detecting neuronal responses have already been identified in the supplementary eye field (SEF) of monkeys trained to perform the antisaccade task (Amador et al., 2000; Amador, Schlag-Rey, & Schlag, 2004).

5.4.3 Conclusions

In this study, healthy adolescents and adults were tested using a novel, rewarded antisaccade task with reward, neutral, and punishment contingencies. Importantly, age-related differences in the

value of the reward for which subjects were working were minimized, allowing us to examine performance differences with minimal age-related motivational confounds.

We found that adolescent, but not adult, AS error rates were particularly sensitive to the effects of increased reward magnitude. In fact, on trials with the highest reward magnitude at stake, adolescents' performances mirrored adults. These data suggest that the basic underlying pathways between brain systems mediating incentive processing and response suppression are available by adolescence, but that persistent immaturities in reward processing (e.g., sluggish, then overactive response) can result in inconsistent behavioral improvements.

Within the context of a set range of rewards and punishment, we found that adolescents demonstrated greater effects of valence and undermined performance on neutral trials. Adults, on the other hand, showed consistent levels of performance across trial types despite showing sensitivity to valence in reaction time. These results suggest both immaturities in adolescent reward processing (improved performance) and in cognitive control. Together, these results highlight the importance of considering the interaction between rewards and cognitive control during development. Immaturities in reward effects on cognitive control during adolescence may contribute to reward-modulated impulsive decisions and risk taking.

6.0 STUDY 3: REWARD AND PUNISHMENT PROCESSING AND EFFECTS ON BRAIN SYSTEMS UNDERLYING INHIBITORY CONTROL IN ADOLESCENTS AND YOUNG ADULTS

6.1 INTRODUCTION

Motivation is defined as the effort one is willing to exert in order to attain rewards and/or avoid punishments or losses (Schultz, 2000). Generally, incentives with high anticipated value (e.g., large magnitude) result in heightened motivation. Single cell studies with non-human primates have suggested that while reward *value* representations are primarily reflected by activity in neurons in the limbic system (e.g., orbitofrontal cortex), the *motivation* to respond for a reward or to avoid punishment is represented by activity in areas more closely associated with motor function, like premotor areas (Roesch et al., 2003; Roesch et al., 2004). Converging evidence from functional magnetic resonance imaging (fMRI) studies with humans indirectly support these distinctions, with consistent reports of reward value-related signaling in OFC and ventral striatum (VS) (Hare et al., 2008; O'Doherty, 2004; Rolls, 2000), as well as effects of motivation in parietal and prefrontal cortex, including premotor regions (Locke & Braver, 2008).

The developmental fMRI reward literature has thus far focused on differences in reward or punishment representations in reward-related brain systems (OFC, VS, medial PFC), finding key age-related differences in both anticipatory and consummatory signaling (May et al., 2004;

van Leijenhorst et al., 2006; Bjork et al., 2007; Bjork et al., 2004; Ernst et al., 2005; Eshel et al., 2007; Galvan et al., 2006). However, age-related differences in the motivation induced by incentives have largely been understudied. Motivation induced by incentives is an important signal to consider empirically in that it may represent a second source of variability contributing to poor decision-making and risk taking (Ernst & Paulus, 2005). The rewarded antisaccade (AS) task is a particularly effective paradigm to study this aspect of reward processing in adolescents and adults given that the brain regions required to support the saccade motor response, the cortical eye fields (CEF; including frontal eye field (FEF), supplementary eye field (SEF), and posterior parietal areas near the intraparietal sulcus), have been exceptionally well-characterized at the single-unit level in non-human primates (Munoz et al., 2004) as well as the circuit level in humans using fMRI (Brown, Vilis, & Everling, 2007; Luna et al., 2001). Thus, differential modulation in these regions (CEF) during anticipatory processing of valenced trials may provide clues on the maturation of motivation-related signaling.

In this study, twenty-eight healthy adolescents and adults (who also participated in study 2) underwent fast, event-related fMRI while performing a modified rewarded antisaccade task with fixed-magnitude incentive cues (5-point potential gain and punishment/loss trials). These cues, along with various pre-test measures intended to minimize incentive value differences, were found to result in equivalent behavioral performances in adolescents and adults (study 2). In this manner, we held performance levels constant while examining similarities and differences in reward-related brain systems (e.g., OFC, VS), presumed to contribute to value representations, and oculomotor control regions (e.g., cortical eye fields), presumed to more closely reflect motivation. Importantly, our experimental design incorporated partial 'catch' trials and jittered

inter-trial fixation periods (as in study 1), enabling us to examine the response in these brain regions during distinct trial epochs (Ollinger et al., 2001b; Ollinger et al., 2001a).

Moreover, our AS task design enabled us to more completely characterize developmental similarities and differences in the neural circuitry recruited in response to feedback. In this study, subjects' saccadic responses were scored in real-time during imaging and auditory, performance-based feedback was immediately provided to the subject during the saccade response epoch. Brain regions of particular interest during feedback processing include the ventral striatum (VS), which is reportedly heightened during adolescent consummatory processing (Ernst et al., 2005), as well as the anterior cingulate cortex, known to support computations underlying response outcome and conflict monitoring (Carter, Botvinick, & Cohen, 1999; Botvinick, Nystrom, Fissell, Carter, & Cohen, 1999; Ridderinkhof et al., 2004).

We hypothesized that both adolescents and adults would engage a similar distributed circuitry to support reward processing and oculomotor control, but that adults would show earlier engagement of oculomotor regions reflective of more efficient information transfer between the widely distributed reward and oculomotor systems (Luna et al., 2004). We also hypothesized that any age-related differences in the cortical eye fields would be most evident on reward or punishment trials but not neutral trials, reflecting differences in motivated (i.e., gain rewards, avoid losses) performance. Furthermore, we hypothesized that during feedback adults and adolescents would engage a largely similar circuitry including VS given that both age groups heard the same correct feedback sound (only correct trials were analyzed in this study). However, adolescents were predicted to show greater feedback-related activity in anterior cingulate (DMPFC) during neutral and punishment trials, reflecting immature assessment of

conflict between the auditory 'reward' tone (indicating a correct response) and the valence of the trial.

6.2 METHODS

6.2.1 Participants

Fourteen adolescents (13-17 years, M = 15.5 (SD = 1.5), 6 females) and fourteen adults (18-26 years, M = 21.6 (SD = 2.3), 9 females) who participated in study 2 also participated in this study. All subjects had far visual acuity of at least 20/40 (corrected or uncorrected) and interview-based medical histories that revealed no neurological disease, brain injury, and no history of personal or first degree relative major psychiatric illness. Age ranges for each group were selected based on previous work indicating differential behavioral performance levels on the antisaccade task at different developmental stages (Luna et al., 2004). Participants and/or their legal guardians provided informed consent or assent prior to participating in this study. All experimental procedures in 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. IQ (Wechsler Abbreviated Scale of Intelligence, 2-part) and indices of socio-economic status (SES; maternal and paternal education level, income) were also collected for each subject.

6.2.2 Eye Tracking

Subjects were first tested in our behavioral laboratory to assure they understood and were able to perform the task as described (see study 2). In the MR scanning environment, eye movements were obtained with a long-range optics eye-tracking system (Model 504LRO; Applied Science Laboratories, Bedford, MA, USA) that recorded eye position by pupil-corneal reflection obtained by a mirror mounted on the head coil with a resolution of 0.5 degrees of visual angle. Simultaneous video monitoring was also used to assure task compliance during the session. At the beginning of each eye-tracking session and between runs when necessary, a nine-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. Eye data were scored off-line using ILAB software (Gitelman, 2002) and an in-house scoring suite written in MATLAB (Math Works, Inc.) running on a Dell Dimension 8300 PC.

6.2.3 Bars Antisaccade Task

Prior to the experimental session, each subject completed a brief questionnaire asking them to choose one of several potential rewards ($25.00 gift cards or a pre-paid debit card) for which they would be working. In this manner, each participant chose a reward that they subjectively deemed to have the highest relative value. Subjects were also asked to rate how ‘valuable’ (7-point Likert scale) they considered their chosen card to be and to write down at least one item that they might purchase with it as a means to increase the salience of the reward. Subjects were instructed that they could win (rewarded trials) or lose (potential loss trials) points on each trial depending on their performance and that these points would be tallied at the end of the session.

Subjects were remunerated based on the proportion of points earned out of a total of 280 using the following scale: 0-70 points (US $10), 71-140 (US $15), 141-210 (US $20), 211-280 (US $25.00 or the chosen gift card).

During the task, subjects were presented with one of three incentive cues (1.5 sec) displayed at the start of each antisaccade trial (see Figure 21). Five green bars above a central fixation indicated to the subject that points would be earned if the trial was corrected performed. Five red bars below the fixation indicated to the subject that points would be lost if an error was generated. Filled gray bars above and below the central fixation indicated that no points were at stake on that trial. Next, the incentive cue disappeared and the fixation cross changed from white to red and was displayed for 1.5 sec. Finally, a peripheral stimulus (yellow dot) appeared (75 msec) at an unpredictable horizontal location (± 4 and 8 degrees visual angle). Subjects were instructed not to look at the stimulus when it appeared but instead direct their eyes to the mirror location.

Eye movement data acquired in the MR environment were scored on-line during the saccade response epoch via an in-line E-Prime script. If at anytime during the first 1000msec of the response epoch the subject generated an eye movement toward the peripheral target, or if no eye movement was generated, an auditory tone (1163Hz peak frequency; 'D') was played for 400msec to indicate an incorrect response. If the subject looked toward the mirror location of the target during this 1000msec window, a 400msec sound of a cash register ('cha-ching') was played (1516Hz peak frequency, 'F-sharp'), indicating a correct antisaccade response. Auditory tones were modified using Audacity, an open-source sound editing program (http://audacity.sourceforge.net).

6.2.4 fMRI: Task Design

As in study 1, the bars antisaccade task consisted of compound trials with an invariant sequence of components (i.e., motor response always follows response preparatory period, which always follows the cue). To separately estimate the hemodynamic response to each epoch, we included approximately 30% partial or "catch" trials, randomly inserted, and jittered inter-trial intervals (see Study 1, Methods) (Ollinger et al., 2001b; Ollinger et al., 2001a). In sum, there were 14 complete reward trials (with 6 catch trials), 14 complete neutral trials (6 catch trials), and 14 complete punishment trials (6 catch trials) per run. Each run lasted 7 minutes 33 seconds. Four runs (trials randomly ordered per run) were presented per session.

6.2.5 fMRI: Image Acquisition and Preprocessing

Imaging data were collected using a 3.0 Tesla Siemens Trio scanner at the Magnetic Resonance Research Center (MRRC), Presbyterian University Hospital, Pittsburgh, PA. A gradient-echo echo-planar imaging sequence sensitive to blood-oxygen-dependent (BOLD) contrast (T2*) was performed (Kwong et al., 1992; Ogawa et al., 1992). The acquisition parameters were: TR = 1.5 sec; TE = 25 ms; flip angle = 70 degrees; single shot; full k-space; 64 x 64 acquisition matrix with FOV = 20 x 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 x 3.125 x 4 mm voxels, which covered the entire cortex and most of the cerebellum. A three-dimensional volume magnetization prepared rapid acquisition gradient echo (MP-RAGE) pulse sequence with 192 slices (1 mm slice thickness) was used to acquire the structural images in the sagittal plane.

Functional images were preprocessed using FMRIB Software Library (FSL) (Smith et al., 2004). 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. Slice timing correction was performed to adjust for sequential slice acquisition. For each subject, translational and rotational movements were averaged across images and used to calculate total root mean square (RMS) movement measures. Subjects that moved more than 1 mm (translational) or 1 degree (rotational) were excluded from additional analyses.

Structural images (MPRAGE) were affine registered to functional images and transformed to the same dimensions using the FLIRT utility available in FSL (Jenkinson et al., 2001). Brain extraction was performed using the brain extraction tool (BET) in FSL (Smith, 2002). Images were spatially smoothed with a 5 mm Full-Width at Half Maximum (FWHM) kernel and subjected to high-pass temporal filtering (sigma = 37.5 sec) to remove low frequency scanner drift. Finally, signal intensity for each run was scaled to a mean of one-hundred and multiple runs were concatenated.

Individual subject deconvolution analyses were conducted using AFNI (Analysis of Functional Neuro-Images) (Cox, 1996), following steps delineated by Ward (1998). Briefly, our model consisted of nine orthogonal regressors of interest (reward, punishment, and neutral cue, preparation, and saccade for correct trials), as well as regressors for reward, punishment, and neutral error trials (consisting of the entire trial; not analyzed in this study), dropped trials (when eye tracking was unclear), baseline, linear, and non-linear trends, and six motion parameters included as 'nuisance' regressors. Sine basis functions were used to estimate the hemodynamic response to the various stimuli of interest (Johnstone et al., 2007). The hemodynamic response function (i.e., estimated impulse response function) for each regressor of interest was determined

by a weighted linear sum of five sine basis functions (each of different frequency) multiplied by a data determined least squares estimated beta weight:

$$h(t) = ß_0 * \sin\{ q * pi * (t - b)/(c-b) \} + ß_1 * \sin\{ q * pi * (t - b)/(c-b) \} + ß_2 * \sin\{ q * pi * (t - b)/(c-b) \} + ß_3 * \sin\{ q * pi * (t - b)/(c-b) \} + ß_4 * \sin\{ q * pi * (t - b)/(c-b) \}$$

where h(t) is the estimated impulse response function at time t, ß = beta value, q = number of basis function (0-4), b = start of modeled response relative to stimulus onset (0 sec), c = end of modeled response relative to stimulus onset (18 sec). In this manner, we specified the duration of the response (18sec) for each regressor but did not make assumptions about its specific shape beyond initial amplitude of zero. Several goodness-of-fit statistics were calculated including partial F-statistics for each regressor and t-scores comparing each of the five estimated beta weights to zero. Two-dimensional images were generated using AFNI.

6.2.6 Group-level Statistical Analyses

6.2.6.1 Anatomical Regions of Interest (ROI)

We examined functionally-defined clusters located within several a priori anatomical regions of interest identified in previous work as serving putative roles in various aspects of reward and/or punishment processing or inhibitory/oculomotor control. Anatomical ROI were the same as reported in Study 1 (Reward-related: ventral striatum (including nucleus accumbens), orbitofrontal cortex, ventral medial prefrontal cortex (VMPFC), and dorsal medial prefrontal cortex (DMPFC); Oculomotor/Inhibitory control: frontal eye field (FEF), supplementary eye

field (SEF), posterior parietal cortex, including areas near the intraparietal sulcus (IPS), putamen, and dorsolateral prefrontal cortex (DLPFC), including BA 9, 46). In addition, we also examined the amygdala and parahippocampal gyrus, as these regions have been shown to be sensitive to punishment (Elliott et al., 2003), as well as the dorsal striatum (caudate), as this region has been linked with feedback processing, magnitude manipulations, and valence (Delgado et al., 2000; Tricomi, Delgado, & Fiez, 2004; Delgado et al., 2003).

6.2.6.2 Time Course Analysis

Estimated impulse response values obtained from each subject's deconvolution analysis were entered into an omnibus voxel-wise ANOVA with time (0 through 12 TR), incentive type (reward, neutral, punishment), and age-group (adolescent, adult) as fixed factors and subjects as the random factor. Separate ANOVAs were run for each trial epoch, resulting in 'cue', 'response preparation', and 'saccade response' group images ('main effect of time' images). A 'main effect of time' image shows regions that are significantly modulated across time (0-12 TR) relative to baseline, across subjects and incentive type, therefore delineating the basic circuitry recruited in our study.

Within each 'main effect of time' image, functionally-defined clusters were identified using methods similar to previous reports (Velanova et al., 2008; Wheeler et al., 2005). 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 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 18 contiguous voxels (486 ml) 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 regions of interest (referred to as 'clusters' below) were defined by including all of the voxels that fell within the 9 mm sphere centered on maximum in the uncorrected image, then excluding those voxels that failed to pass corrections for multiple comparisons. We then used these functionally defined ROI as masks and extracted the estimated time courses from the constituent voxels from each subject and across incentive conditions. Time courses were averaged across subjects and analyzed for age- and incentive-related effects with repeated measures ANOVA in SPSS; age group (adult, adolescents) served as the between subjects factor; time (0 - 12 TR) and incentive condition (reward, punishment, neutral) were within subjects factors.

The main comparisons of interest in this study were the two- and three-way interactions with age (valence by age, time by age, and valence by time by age interactions). To further delineate the nature of significant age-related effects identified in the omnibus ANOVA, separate repeated measures ANOVAs, with time (0-12 TR) as the within-subject factor and age group as between subject factor, were also conducted for each incentive trial type. These effects are reported below immediately following the omnibus ANOVA effects.

Where indicated, Greenhouse-Geisser (G-G) levels of significance are reported if sphericity assumptions were violated (as determined by a significant Mauchley's test of sphericity). 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).

6.2.7 Separate Age Group Images

While developmental differences may be evident in the age group effects, it is valuable to also examine separate age group 'main effect of time' maps as a means to examine similarities in recruited circuitry. To qualitatively assess brain activity patterns across age groups for each incentive type and trial epoch, mixed-effects analyses of variance (ANOVA), with time (0 - 12 TR) as a fixed factor and subjects as a random factor, were run using the estimated impulse response values obtained from individual subjects' deconvolution analyses. Separate 'main effects of time' maps were generated for each age group and incentive trial type (reward, punishment, neutral) for each of the three epochs of the trial (cue, response preparation, saccade response).

6.3 RESULTS

6.3.1 Participants

As determined by the Wechsler Abbreviated Scale of Intelligence (WASI; 2-part), IQ's for both adults and adolescents were in the normal range (adult, M = 123.33, SD = 5.23; adolescent, M = 109.5, SD = 11.28). Adults and adolescents in this sample did not differ on the various socio-economic indices obtained, including maternal education, paternal education, maternal income, or paternal income (all p's >0.05).

The large majority of subjects chose a pre-paid debit card as their selected reward (12 of 14 adolescents and 13 of 14 adults). Adolescents and adults did not differ in how valuable they

rated (7-point Likert scale) their selected reward or in their subjective ratings of how they felt when seeing and hearing the reward and punishment cues and feedback sounds, as assessed by pre- and post-test questionnaires (all p's > 0.05).

6.3.2 Behavioral

By design, no significant main effects of age or incentive type (reward, punishment, neutral) or age group by incentive interactions were observed for prosaccade error rates or latencies of prosaccade errors (Figure 22). For correct antisaccade latencies, we did observe a main effect of incentive type ($F(2,50)=4.465$, $p=0.026$ (Greenhouse-Geisser corrected level of significance). Post hoc contrasts showed that latencies for reward trials were significantly faster than punishment trials ($F(1,25)=4.261$, $p=0.05$), but punishment latency values did not differ from neutral trials ($p>0.05$). However, no age group by valence interaction was observed for correct antisaccade latencies ($p>0.05$).

6.3.3 fMRI

As in Study 1, a widely distributed network of brain regions was engaged across each epoch of the task by both adults and adolescents, including canonical oculomotor/ inhibitory control areas (e.g., cortical eye fields, lateral prefrontal cortex, basal ganglia), as well as expected reward-related brain systems (e.g., VMPFC, OFC, VS) (Figures 23 and 24).

Below, we identify various functional ROI's (i.e., 'clusters') identified in the omnibus ANOVA 'main effect of time' images (cue, preparation, and saccade response) that exhibited age-related effects. These effects are summarized in Tables 5-7. Time courses for each of these

regions are presented in Figures 25 (cue/incentive assessment), 26 (response preparation/incentive anticipation), and 27 (saccade response/feedback).

6.3.3.1 Cue / Incentive Assessment

Incentive-Related Regions

During the presentation of the incentive cue, when the incentive is initially detected and assessed (i.e., the subject determines whether he or she has the potential to gain points (reward), lose points (punishment), or stay the same (neutral)), we observed a single cluster in right lateral orbitofrontal cortex (OFC) (41, 40, -2) showing a time by age interaction *(F(12,312)=2.066, p=0.019)*. Adolescents recruited this region to a greater extent compared to adults, primarily during punishment trials *(age by time interaction, F(12,312) = 2.643, p=0.002).* Adolescents also strongly recruited this area during neutral trials, but no significant age-related differences were observed *(p=0.090).* Time courses from this region are shown in Figure 25.

Oculomotor and Inhibitory Control Regions

Overall, adults showed heightened activity in response to the incentive cue in the cortical eye fields. Compared to adolescents, adults showed greater responses in two FEF loci *[R FEF (44, -5, 46): main effect of age (F (1, 26) = 8.708, p=0.007); neutral trials: main effect of age, F(1, 26) = 4.758, p=0.038)], [R FEF, 2nd Cluster, (32, -11, 43): main effect of valence (F(2, 52) = 5.092, p=0.010), valence by age interaction (F(2, 52) = 5.997, p=0.005), valence by time by age interaction (F(24, 624) = 2.423, p<0.001); reward trials: age by time interaction (F(12, 312)=3.462, p<0.001); punishment trials: main effect of age (F(1, 26) =5.564, p=0.026)]*. Similarly, adults recruited SEF more than adolescents during reward and punishment cues *[L SEF (-1, 4, 46): valence by age interaction (F(2, 52)=4.735, p=0.013), main effect of age (F(1,*

26)=5.662, p=0.025); reward trials: age by time interaction (F(12, 312) = 2.017, p=0.022); punishment trials: main effect of age (F(1,26) = 11.495, p=0.002)]. Finally, adults also showed greater activity in superior parietal lobule during punishment trials *[L SPL (-28, -62, 40): main effect of valence (F(2, 52) = 4.063, p=0.023), valence by time interaction (F(24, 624) = 3.466, p<0.001), main effect of age (F(1, 26) = 4.621, p=0.041); punishment trials: main effect of age (F(1, 26) = 6.756, p=0.015)]*.

Time courses from each of these regions are shown in Figure 26.

6.3.3.2 Response Preparation / Incentive Anticipation

Incentive-Related Regions

During the response preparation period, subjects anticipated responding in order to gain points, avoid losing points, or to maintain their current point level. Adults showed increased recruitment of OFC compared to adolescents *[L OFC, BA 47/11, (-37, 31, -5): valence by time interaction (F(24, 624) = 2.180, p=0.001), valence by time by age interaction (F(24, 624) = 2.706, p<0.001); reward trials: age by time interaction (F(12, 312) = 4.407, p<0.001)]*. Adolescents, however, showed a temporally prolonged response in this region during punishment anticipation *[L OFC, BA 47/11, (-37, 31, -5): punishment anticipation age by time interaction, (F(12, 312) = 1.907, p=0.033)]*, as well as in a more anterior OFC location *[R OFC, BA 10/11, (26, 46, -5): valence by time by age interaction (F(24, 624) = 1.671, p=0.024); punishment trials: age by time interaction (F(12, 312) = 1.892, p=0.035)]*. Similarly, adolescents also demonstrated stronger recruitment of anterior cingulate (DMPFC) compared to adults during punishment anticipation *[R DMPFC, BA 24/32, (8, 22, 22): valence by time interaction (F(24, 624) = 1.596, p=0.036), valence by time by age interaction (F(24, 624) = 1.942, p=0.005); punishment trials: age by time interaction (F(12, 312) = 1.883, p=0.036)]*.

Time courses from each of these regions are shown in Figure 27.

Oculomotor and Inhibitory Control Regions

During the response preparation/anticipation epoch, adolescents consistently showed temporally prolonged responses during punishment trials in oculomotor/inhibitory control regions compared to adults. For instance, adolescents showed greater recruitment of SEF compared to adults *[R SEF (8, 4, 49): main effect of valence ($F(2, 52) = 3.834$, $p=0.028$), valence by time by age interaction ($F(24, 624) = 2.089$, $p=0.002$), main effect of age ($F(1, 26) = 5.233$, $p=0.031$); punishment trials: main effect of age ($F(1, 26) = 8.701$, $p=0.007$); reward trials: age by time interaction ($F(12, 312) =2.009$, $p=0.023$)]*. Adolescents also showed more pronounced recruitment in a posterior area of the FEF *[R FEF, BA 6/9 (44, 1, 34): main effect of valence ($F(2, 52) = 5.862$, $p=0.005$), valence by time interaction ($F(24, 624) = 1.667$, $p=0.024$), valence by time by age interaction ($F(24, 624) = 2.483$, $p<0.001$), main effect of age ($F(1, 26) = 5.461$, $p=0.027$); punishment trials: main effect of age ($F(1, 26) = 4.864$, $p=0.036$); reward trials: age by time interaction ($F(12, 312) = 3.548$, $p<0.001$)]*.

In posterior parietal regions, adolescents showed similar prolonged responses during punishment trials, as well as increased activity during rewarded trials, compared to adults. For instance, adolescents showed heightened responses compared to adults in left superior parietal lobule *[L SPL, BA 7, (-25, -59, 40): main effect of valence ($F(2, 52) = 8.934$, $p=0.001$) (G-G), main effect of age ($F(1, 26) = 4.921$, $p=0.035$)]*. In this region, differential responses across time were observed during neutral trials *(age by time interaction, $F(12, 312) = 2.247$, $p=0.010$)* and qualitatively greater adolescent responses were observed during punishment trials *($p>0.05$)*. Adolescents also showed greater activity in the precuneus compared to adults during reward and

punishment anticipation *[R Precuneus, BA 7, (5, -62, 52): valence by time by age interaction (F(24, 624) = 1.740, p=0.016); reward trials: age by time interaction (F(12, 312) = 2.434, p=0.005)], [L Precuneus, BA 7, (-1, -56, 43): main effect of valence (F(2, 52) = 5.158, p=0.009), valence by time interaction (F(24, 624) = 2.050, p=0.002), valence by time by age interaction (F(24, 624) = 3.155, p<0.001); reward trials: age by time interaction (F(12, 312) = 2.469, p=0.004); punishment trials: age by time interaction (F(12, 312) = 2.491, p=0.004)]*. Finally, adolescents also showed a more defined, canonical response during reward trials in the right superior occipital gyrus *[R SOG (20, -62, 34): main effect of valence (F(2, 52) = 4.215, p=0.020), valence by time interaction (F(24, 624) = 2.397, p<0.001, valence by time by age interaction (F(24, 624) = 1.857, p=0.008); reward trials: age by time interaction (F(12, 312) = 2.329, p=0.007)]*.

Time courses from each of these regions are shown in Figures 28 and 29.

6.3.3.3 Saccade Response / Feedback

Incentive-Related Regions

During the saccade response epoch, subjects generated a correct antisaccade and heard auditory feedback. Adults showed a greater response than adolescents in the ventral striatum during reward trials *[L VS (-13, 16, -2): main effect of age (F(1, 26) = 4.176, p=0.05); reward trials: main effect of age (F(1, 26) = 8.167, p=0.008)]*. Adolescents showed a greater response compared to adults in the left anterior cingulate *[L DMPFC, BA 32/24, (-7, 31, 22): time by age interaction (F(12, 312) = 2.274, p=0.009), trend towards a valence by time interaction (F(24, 624) = 1.505, p=0.058); neutral trials: age by time interaction (F(12, 312) = 2.104, p=0.016)]*. In amygdala, adolescents and adults showed approximately similar initial peaks across trial types, but the adolescents' responses were characterized by a more negative-going dip before

returning to baseline *[L Amygdala (-25, -2, -14): time by age interaction (F(12, 312) = 4.039, p<0.001) and a main effect of age (F(1, 26) = 9.529, p=0.005); punishment trials: age by time interaction (F(12, 312) = 2.894, p=0.001); neutral trials: age by time interaction (F(12, 312) = 1.753, p=0.055)], [R Amygdala (29, -8, -14): time by age interaction (F(12, 312) = 3.232, p<0.001); reward trials: age by time interaction (F(12, 312) = 2.439, p=0.005), main effect of age, F(1,26) = 8.436, p=0.007); neutral trials: age by time interaction (F(12, 312) = 1.959, p=0.027)]*.

Time courses from these regions are shown in Figure 30.

Oculomotor and Inhibitory Control Regions

Overall, adults showed greater recruitment of the cortical eye fields during valenced (reward, punishment) trial responses and feedback. For instance, adults showed heightened responses during reward trials in multiple FEF loci *[R FEF (20, -8, 55): main effect of valence (F(2, 52) = 3.098, p=0.054), valence by time by age interaction (F(24, 624) = 1.580, p=0.039); reward trials: age by time interaction, F(12, 312) = 2.550, p=0.003); punishment trials: age by time interaction (F(12, 312) = 2.219, p=0.011)], [R FEF 2nd cluster (41, -11, 46): valence by time by age interaction (F(24, 624) = 2.018, p=0.003); reward trials: age by time interaction (F(12, 312) = 2.224, p=0.011)], [L FEF (-34, -8, 46): main effect of valence (F(2, 52) = 3.354, p=0.043), valence by time by age interaction (F(24, 624) = 1.546, p=0.047); reward trials: main effect of age (F(1, 26) = 4.154, p=0.05)]*. The SEF was also recruited more by adults than adolescents, during reward and punishment trials *[L SEF (-4, -8, 55): time by age interaction (F(12, 312) = 2.151, p=0.014), valence by time interaction (F(24, 624) = 1.850, p=0.008), valence by time by age interaction (F(24, 624) = 1.557, p=0.044); reward trials: age by time*

interaction (F(12, 312) = 2.704, p=0.002); punishment trials: age by time interaction (F(12, 312) = 2.691, p=0.002)].

Regions in posterior parietal cortex showed a similar increased recruitment in adults compared to adolescents during reward and punishment trials *[R SPL, BA 7, (20, -62, 49): valence by time interaction (F(24, 624) = 1.853, p=0.008), valence by time by age interaction (F(24, 624) = 1.583, p=0.039), main effect of age (F(1, 26) = 5.179, p=0.031); reward trials: age by time interaction (F(12, 312) =1.998, p=0.024)], [R IPL, BA 7, (26, -47, 43): main effect of age (F(1, 26) = 4.914, p=0.036); punishment trials: main effect of age (F(1, 26) = 4.504, p=0.044)].*

Finally, adolescents showed greater activation in the thalamus *[R thalamus (2, -20, 4): time by age interaction (F(12, 312) = 3.166, p<0.001); reward trials: age by time interaction (F(12, 312) = 3.476, p<0.001)], [L thalamus (-16, -20, 10): trend toward a time by age interaction (F(12, 312) = 1.771, p=0.052), valence by time interaction (F(24, 624) = 1.737, p=0.016); neutral trials: time by age interaction (F(12, 312) = 2.646, p=0.002)].*

Time courses from each of these regions are shown in Figures 31 and 32.

6.3.4 Valence- and Time-related Effects

A number of regions were recruited during the task that only showed time or valence-related effects (main effect of time, main effect of valence, or valence by time interactions) (summarized in Tables 8-10). These regions are presumably functioning at mature (adult) levels during adolescence. The time courses showing how each of these commonly recruited regions varies across trial types and time for each trial epoch are provided in Figures 33-44.

Of primary interest were the observed similarities across age groups in the ventral striatum during the cue and response preparation epochs, particularly given our previous results (study 1) indicating differences in the temporal activation of this region (adults activated the VS during the cue, while adolescents strongly engaged this region during the preparatory period).

During the incentive cue epoch in the current task, the right ventral striatum (5, 10, -8) was recruited earlier and reached a higher peak magnitude during reward trials compared to punishment and neutral (Figure 45). Interestingly, adults showed a qualitatively earlier peak than adolescents in this region during reward trials, although a t-test comparing time to peak did not reach significance. In contrast, during response preparation/incentive anticipation, the ventral striatum showed a main effect of time, but no age- or valence-related effects, indicating similar responses in this region across age groups and conditions.

6.4 DISCUSSION

In this study, healthy adults and adolescents underwent fast, event-related fMRI as they performed an incentive-mediated antisaccade task with a reward, punishment, or neutral contingency on each trial. We used fixed, relatively high magnitude (5-point) incentive stimuli and controlled for differences in incentive value, methods previously determined to result in equivalent behavioral performances across the age groups (study 2). Our fMRI task design enabled us to examine the circuitry recruited at different temporal stages of the task. In this manner, we were able to characterize developmental similarities and differences in brain systems presumed to code anticipatory signals like value and motivation, as well as consummatory signals like feedback. Overall, while both age groups recruited a similar circuitry to support task

performance across trial type, a number of brain regions demonstrated age- and valence-related differences in their hemodynamic time courses suggesting differences in their underlying function. These effects are discussed in more detail below.

6.4.1 Developmental Differences in Reward-related Brain Regions

A region in right lateral OFC (BA 10, 47) was recruited more strongly by adolescents compared to adults during punishment and neutral cues. Activation in lateral OFC has been reported to represent monetary punishment or loss (O'Doherty et al., 2001; Rolls, 2000). Our results could indicate that adolescents, more so than adults, form early judgments of punishment and neutral trials as being particularly unpleasant in this task, perhaps because on these trials no gains are made toward their chosen reward.

Additional age-related differences were evident later in the trial. During the preparatory period, adults recruited a region along the inferior frontal gyrus (OFC, BA 47, 11) more than adolescents during reward trials supporting our findings from study 1 as well as other developmental studies (Galvan et al., 2006; Ernst et al., 2005). Inferior frontal gyrus has been associated with inhibitory control (Chamberlain & Sahakian, 2007) as well as representations of incentive value (Rolls, 2000). In adults, this region may have been engaged to enhance inhibitory control during trials on which points could be gained. Adolescents showed a similar, prolonged response during punishment trials in this region, as well as in right OFC (BA 10, 11), and in the right anterior cingulate (DMPFC, BA 23, 32). The anterior cingulate has been consistently implicated in response/conflict monitoring (e.g., Botvinick et al., 2001). Our results suggest that during the response preparation/incentive anticipation epoch, adolescents have a heightened

anticipation of potential losses and may be monitoring their own performance more on punishment trials in order to avoid losses (Bengtsson, Lau, & Passingham, 2009).

Following a correct antisaccade eye movement and hearing the auditory tone ('cha-ching'), adults showed a greater response in rostral ventral striatum during reward trials. This result was somewhat surprising given previous reports of adolescent over-activity during consummatory processing in this region (Ernst et al., 2005). However, previous work did not account for differences in monetary value across age group. Taking into consideration results from the response preparation/anticipation phase, our data suggest that from adolescence to adulthood there may be a shift from reward systems supporting anticipation to supporting outcome. In an indirect manner, these results can be seen displayed in risk taking behavior, where adolescents do not consider the outcome as much as adults but are seemingly driven by anticipation of the reward.

The anterior cingulate (ACC) was more strongly recruited by adolescents during neutral trial feedback. This may reflect that in the context of this experiment, where different valence conditions were presented in a random fashion, adolescents may have to invest in performance monitoring, supported by ACC, in the neutral trials to ensure that it is not a valenced trial. Adults' mature cognitive system may allow them to assess this discrepancy more readily, not needing to engage ACC.

Finally, bilateral amygdala was also differentially engaged in adolescents and adults during the saccade response/feedback epoch. While amygdala recruitment was roughly equivalent for adults and adolescents with regards to reward processing, adults showed slightly greater recruitment during punishment trials. Studies in which incentive value differences have not been accounted for show increased responses in amygdala during reward feedback in adults

compared to adolescents (Ernst et al., 2005). Given our methods, these results suggest that when minimizing reward value the amygdala is recruited similarly across ages. The amygdala has been implicated in the emotional processing of stimuli, most notably faces, but has been shown to be sensitive to reward (positive) and punishment (negative) feedback (Zalla et al., 2000; Ernst et al., 2005). Increased recruitment by adults during punishment trials may indicate that adolescents may have immaturities in emotional processing when correctly avoiding a loss.

6.4.2 Developmental Differences in Oculomotor/Inhibitory Control Brain Regions

During valenced conditions (reward, punishment) of the cue epoch, the adult group consistently showed greater peak responses than adolescents in the cortical eye fields (FEF, SEF, posterior parietal cortex). Increased activity in the cortical eye fields underlie the cognitive control of eye movements (Sweeney et al., 1996; Luna et al., 2001; Muri et al., 1996). Age effects were most evident during reward and punishment trials, suggesting different levels of motivation in these regions. More specifically, adults may show increased gain in the cortical eye fields during the initial presentation of the incentive cue in anticipation of responding to acquire or avoid losing points. Importantly, increased activity during valenced compared to neutral trials provides further support that adults were indeed sensitive to the valence conditions (see study 2, discussion). The under-activity during this early stage of reward processing in adolescents points to a different approach in planning oculomotor responses.

Later during the response preparation epoch, adolescents showed evidence of enhanced motivational processing in oculomotor regions, particularly during punishment trials. Adolescents showed a consistent prolonged hemodynamic response during punishment trials in the cortical eye fields, very similar to their responses in OFC and anterior cingulate noted above.

Adolescents also showed increased activity during the preparatory period of reward trials, but only in posterior parietal areas like the precuneus. Thus, adolescents show increased gain in regions involved in generating the motor response, but do so later in a trial than adults, during response preparation, particularly in anticipation of responding to avoid a point loss. These results suggest that adolescents may demonstrate immature processing of potential losses or risk (here, the risk is potentially losing points), requiring extra 'effort' in the form of heightened activity in order to achieve adult-like levels of behavior (Luna et al., 2001). A 'risk anticipation' system operating at such a high capacity may be more prone to perturbation and errors, similar to the effects of increased cognitive load on antisaccade performance (Stuyven, Van der Goten, Vandierendonck, Claeys, & Crevits, 2000), and could contribute to vulnerabilities to poor decision-making and risk taking during adolescence. Alternatively, the later recruitment of oculomotor regions by adolescents may reflect immaturities in the circuitry supporting cognitive control of eye movements that delay their incorporation in response planning.

During the saccade response/feedback epoch, adults showed increased activity primarily during reward trials bilaterally in FEF, left SEF, and in right superior parietal lobule. Increased adult responses were also observed during punishment trials in a right FEF cluster, the SEF, and right inferior parietal lobule. Enhanced activity in these brain areas could reflect the outcome of increased motivational processing, discussed above. Alternatively, increased activity in these areas, particularly the SEF, may also reflect more refined feedback-related processing in adults, including monitoring the context and consequences of eye movements that resulted in point gain (Schall, Stuphorn, & Brown, 2002). As noted above, there may be developmental differences in the timing of reward reactivity where adolescents peak during reward anticipation and adults peak during reward receipt. This interpretation may shed light into how adolescents' risk taking

behavior can be seen as being driven by the anticipation of a response with less regard to outcome, while the mature adult system is more invested in the actual outcome.

6.4.3 Anticipatory Processing in Ventral Striatum

One striking difference between the results of this study and previous work (study 1) was the differential recruitment of the ventral striatum. In study 1, we found that adults but not adolescents activated the ventral striatum during presentation of a reward cue. Later, during response preparation of rewarded trials, adolescents activated the VS to a higher magnitude than adults. We interpreted the results from study 1 as indicating that components of the adolescent reward system show an initial delay in recruitment, then over-activity once engaged compared to adults. In the current study, however, we found no differences in VS recruitment across the age groups during the cue or response preparation epochs. These findings may stem from the measures used to minimize differences in incentive value. Given that minimizing value differences across the age groups resulted in similar recruitment of VS suggests that this system can process reward contingencies in a mature manner; what changes developmentally then may be the interpretation of value. Alternatively, adolescent recruitment of VS may have been attenuated due to the context of different valenced trials. In the current study, reward, punishment, and neutral trial contingencies were used. In contrast, study 1 examined only reward and neutral trials. Thus, the addition of the punishment condition may have altered the contextual meaning of reward and neutral trials. In study 1, participants could only gain or stay the same (so neutral may have been more 'punishing'), whereas point loss was a third possibility in the current experiment. This framing or contextual effect may have contributed to tempering the adolescents' exuberance and over-activity in VS during reward trials.

6.4.4 Conclusions

During an incentive-mediated antisaccade task where equivalent behavioral performance levels were reached, a number of age-related differences were still evident in reward-related and oculomotor/inhibitory control brain regions. Adults showed increased activity relative to adolescents in FEF, SEF, and posterior parietal regions during the presentation of reward and punishment cues, suggesting that adults may be more efficient in their use of detected incentives to motivate behavior. Adolescents showed heightened activity in lateral OFC during punishment and neutral cues suggesting that they were particularly sensitive to non-gain or potential loss trials. Further, adolescents showed increased activity in the cortical eye fields later, during response preparation, and primarily during punishment trials suggesting that adolescents have immaturities in brain systems involved in processing potential losses that could contribute to suboptimal decision-making and risk taking. These results also suggest that the adolescent system can process reward in a similar fashion as adults when age-related differences in value are minimized. Therefore, immaturities in adolescent reward processing may be due primarily to the interpretation of value. Finally, adults were found to demonstrate heightened activity in multiple regions during the response/feedback epoch. Collectively, these age-related differences suggest that adolescent reward processing may be primarily driven by incentive anticipation while adults may be more invested in outcome, which has implications for the more impulsive pursuit of rewards with less regard to outcome that characterizes adolescent risk-taking behavior.

7.0 GENERAL DISCUSSION

The major aims of this dissertation were to better understand similarities and differences in how rewards and punishments are represented in the adolescent brain relative to young adults and examine the influence of incentives on response inhibition, a primary component of the cognitive control of behavior. Toward these ends, three studies were presented each utilizing antisaccade (AS) paradigms with trial-by-trial incentive contingencies that allowed us to simultaneously examine developmental changes in the reward system and effects of incentives on oculomotor control regions supporting behavior. The major findings of these studies are summarized and their implications are further discussed below.

In study 1, fast, event-related fMRI was used to characterize developmental differences in brain systems recruited to support performance on an antisaccade task with reward and neutral trial contingencies. While developmental differences in performance on rewarded antisaccade tasks had been reported behaviorally (Jazbec et al., 2006; Hardin et al., 2007), this study is the first to use fMRI to examine the neural circuitry underlying these effects. Importantly, we utilized a novel, yet empirically validated experimental design that included partial 'catch' trials and jittered inter-trial intervals (Ollinger et al., 2001b; Ollinger et al., 2001a), enabling us to examine the circuitry supporting different trial components and reward signals (cue/reward detection, response preparation/reward anticipation, and saccade response) (Schultz, 2000). Examination of the scanner eye data showed that the AS error rates were lower on rewarded

compared to neutral trials in both age groups, with adolescents showing slightly greater performance gains. fMRI results revealed that adults showed earlier recruitment of ventral striatum and OFC during reward but not neutral cues, suggesting an earlier anticipation and executive assessment (e.g., anticipated value representation) of rewards (O'Doherty et al., 2001). In contrast, adolescents did not show OFC activity during the trial and did not recruit the VS until the response preparation period. However, once the VS was engaged it reached a higher peak magnitude than that observed in adults. These results suggest that components of the adolescent reward system show a delayed but over-active response to reward, helping to resolve a current debate in the literature regarding hypo- vs. hyper-activity in the adolescent VS (Bjork et al., 2004; Ernst et al., 2005). Furthermore, adolescents showed an increase in activity in the FEF and SEF, regions critical to the ability to suppress the reflexive saccade, during the preparatory period of reward trials. This heightened activity in the cortical eye fields provides a plausible mechanism underlying the performance gains evident in adolescents. In sum, study 1 advances our current understanding of the adolescent reward system by identifying specific immaturities in reward-related brain regions involved in the executive assessment (OFC) as well as the anticipation (VS) of future rewards, indicating a delayed, yet over-active response to rewards.

In study 1, a single, unvarying reward cue was used on each trial and money (US $25) was used as motivation. In study 2, we aimed to more completely characterize the influence of varying magnitudes of reward and punishment contingencies on antisaccade performance. For this study, we implemented various pre-test measures (e.g., subjects chose their rewards, a fixed-range point system was established) intended to minimize potentially confounding issues related to how the different age groups value the reward for which they were working, a pervasive yet under-studied issue in the reward literature. Moreover, we included performance-based feedback

that made subjects immediately aware of whether or not they made a correct response. Under these conditions, we found that adults performed consistently well (i.e., low error rates) regardless of incentive trial type. In contrast, adolescent error rates were significantly reduced on high (5 point) compared to low (1 point) magnitude reward trials. On punishment trials, adolescents, like adults, generated similar low error rates across all magnitude levels. Thus, our results indicate that adolescents can perform at adult-like levels on this task, but in certain contexts may require a greater motivational 'push' to do so. This motivational push in study 2 came from the opportunity to win (relatively) high magnitude points on reward trials and the threat of losing any points. More broadly, these behavioral results suggest that the basic circuitry underlying reward modulation of cognitive control is available in adolescence, but the ability to flexibly and consistently utilize this pathway to motivate behavior even when gains are relatively low is not yet mature. These results further suggest that the neural representation of potential losses or 'risk' (or, conversely, the possibility of not gaining the full end reward amount), at least in the context of this study, is heavily weighted in the adolescent brain and significantly affects behavior.

In our third study, fourteen adults and fourteen adolescents who first participated in study 2 underwent fast, event-related fMRI to examine the circuitry supporting performance on an incentive mediated AS task with reward, punishment, and neutral trial contingencies. In this version of the task, high, fixed-magnitude reward and punishment incentive stimuli (5 points - the maximum available in study 2) that resulted in equivalent behavioral performances across the two age groups were used. Additionally, we again controlled for reward value differences and incorporated real-time eye movement scoring that provided immediate feedback to the subjects. As in study 1, our task design enabled us to examine the circuitry recruited at different temporal

stages of the task permitting characterization of brain systems presumed to code anticipatory signals like value and motivation, as well as consummatory signals like feedback.

We found that even when controlling for behavioral performance, a number of age-related differences were still observed. First, adolescents showed increased activity in response to the punishment and neutral cues in lateral OFC, an area consistently engaged to support punishment or loss representations (O'Doherty et al., 2001; Hare et al., 2008). This suggested a heightened sensitivity to potential loss or non-gain cues in adolescents. Adults showed heightened activity in oculomotor control regions (cortical eye fields) primarily during reward and punishment cues, reflecting earlier (and perhaps more efficient) motivational enhancement of regions central to both inhibiting the reflexive response to the peripheral stimulus and generating the volitional saccade to the mirror location. Adolescents also showed motivational enhancements in oculomotor regions, but not until later in the trial during the response preparation epoch. The adolescent motivational response was characterized by greater activity in posterior parietal regions during reward trials (e.g., precuneus) and, most prominently, temporally prolonged responses during punishment trials throughout the cortical eye fields (FEF, SEF, and parietal areas). Increased signaling during punishment trials may explain why adolescents performed at near adult-like levels in study 2, even on low magnitude punishment trials. These results suggest a protracted maturation of motivation signaling and that the adolescent brain may devote additional computational resources to process potential losses or risk when a valued reward is at stake. Previous studies examining aspects of developmental risk processing have tended to focus on activity in dorsolateral prefrontal cortex, anterior cingulate and posterior medial prefrontal cortex (Galvan et al., 2006; Eshel et al., 2007; Bjork et al., 2007; van Leijenhorst et al., 2006). Our results further implicate these regions as well provide evidence

for a more distributed circuitry including the cortical eye fields contributing to the processing of potential loss.

During the saccade response/feedback epoch, adults and adolescents recruited a largely similar circuitry, an expected result given similarities in response demands (an eye movement). However, adults compared to adolescents also showed higher peak magnitudes during reward trials in the ventral striatum and in the cortical eye fields. These effects may have arisen due to more refined, feedback-related processing like monitoring the consequences of actions leading to reward (Schall et al., 2002). These results suggest that while the adolescent system is primarily engaged during response anticipation, the adult system is primarily engaged during reward outcome. The implication is that adolescent risk-taking behavior may be characterized by impulsive reactions to the anticipation of rewards while the mature adult system may be more prone to consider reward outcomes.

Finally, we also found a number of *similarities* between adolescents and adults in terms of their responses to different valenced trials in this task (see Tables 8-10). Specifically, both age groups similarly recruited the ventral striatum during the cue and preparatory periods (see study 3, Discussion). The results from study 3, when taken into consideration with observed age-related differences, highlight a fundamental and recurrent theme of adolescent brain maturation. Namely, while basic systems and the functions they subserve are in place by adolescence (e.g. discriminate rewards and punishments, incentive modulation of behavior), continued refinement of these systems persists into adulthood (e.g., earlier motivational effects on oculomotor regions) (Luna et al., 2001; Luna et al., 2004a; Bunge et al., 2002; Durston et al., 2006). Importantly, our results suggest that primary to what changes from adolescence to adulthood may be a more refined, consistent interpretation of value.

7.1 CONCLUSIONS

In chapter 1, we presented a simple model suggesting that immaturities in reward processing and core cognitive control abilities, like working memory and response inhibition, may collectively underlie sub-optimal decision-making contributing to adolescent risk taking. In this dissertation, we expounded on this basic model by characterizing the nature of specific immaturities in adolescent reward processing and how incentives affect response inhibition circuitry and behavior. Our results indicate that adolescent reward processing is characterized by a delayed, but heightened anticipatory processing of potential rewards, reduced executive assessment of rewards, and increased processing associated with punishment/losses (i.e., risk). Furthermore, our data suggest that the nature of the responses observed in various brain regions (e.g., VS) may be particularly sensitive to contextual influences (i.e., if losses are a possibility) and may be preferentially focused on reward anticipation instead of reward outcome, as seen in adulthood. Immature reward system functioning such as these may expose already present vulnerabilities (i.e., inconsistencies) in a still-maturing adolescent response inhibition system. The consequences for decision-making could be the biased selection of an option associated with a more salient, shorter-term reward outcome – adaptive in some instances, maladaptive in others.

We note that while performance on a rewarded antisaccade task is an abstraction from the complexities of actual adolescent risk taking behaviors (e.g., experimenting with drugs), our results highlight immature function in key brain regions likely to be engaged during more complex behavior. By thoroughly characterizing the response properties of contributing brain systems during simple laboratory tasks, we lay the fundamental groundwork for future studies to test increasingly complex experimental parameters. Importantly, if the circuitry supporting simple tasks, such as the antisaccade task, is immature, then more complex behaviors such as

experimentation with drugs will also likely be undermined. Finally, while it is the case that most adolescents navigate through adolescence without serious issues (Dahl, 2004), by most accounts this period of development represents a peak in the ontology of an individual's novelty- and sensation-seeking, as well as in behavioral impulsivity. Further investigation of adolescent reward processing and incentive influences on cognitive control systems will increase our basic understanding of the extremes of adolescent behavior like risk taking, as well as advance our on-going efforts to establish a normative template of the adolescent's brain and behavior. The aim of the series of studies presented in this dissertation was to move us closer to this ultimate goal.

Table 1: Scanner eye tracking results for reward and neutral antisaccade trials

	Correct Response Rate		Latencies of Correct Antisaccades (msec)		Latencies of Antisaccade Errors (msec)	
Trial	**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)

Table 2: Regions demonstrating a main effect of time in anatomical regions of interest, observed during cue (correct trials only). Regions showing age- and/or incentive-related effects are italicized.

Talairach Coordinates			Region	BA	Peak F	Volume (ml)
x	y	z				
14	2	-7	***Right Ventral Striatum***	**	5.62	270
-10	2	-4	Left Ventral Striatum	**	3.66	135
5	50	11	Right Medial Frontal Gyrus, 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/Medial Frontal Gyrus	9,10	6.49	864
-7	50	8	***Left Medial Frontal Gyrus, 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 Anterior Cingulate VMPFC	24,32	7.86	729
8	41	8	Right Anterior Cingulate, VMPFC	32,10	6.41	783
2	17	32	Right Cingulate Gyrus, Dorsal Medial PFC	32,24	3.48	270
-1	29	17	Left Anterior Cingulate, VMPFC	24,32	6.28	702
-7	41	2	***Left Anterior Cingulate, VMPFC***	32	5.98	810
-1	35	8	Left Anterior Cingulate, VMPFC	24,32	5.91	837
-13	8	38	Left Cingulate Gyrus, Dorsal Medial PFC	32,24	5.13	432
38	-10	44	Right FEF	6	5.91	783
35	-1	41	***Right FEF***	6	5.86	729
26	-13	53	Right FEF	6	4.95	486
41	2	29	Right FEF	6	4.7	486
44	11	32	Right FEF	6,9	4.07	459
-34	-4	35	***Left FEF***	6	6.69	756

-25	-10	50	Left FEF	6	6.63	864
-34	-7	50	Left FEF	6	5.63	324
-46	-7	38	Left FEF	6	3.33	162
-4	-1	53	***Left SEF***	6	10.29	810
29	-61	38	Right Precuneus	7	14.05	891
29	-52	32	Right Precuneus	39	10.31	837
-28	-64	41	Left Precuneus	19, 7	11.16	891
-28	-52	38	***Left Angular Gyrus***	7	12.26	891
41	32	14	Right DLPFC	46	4.71	675

Table 3: Regions demonstrating a main effect of time in anatomical regions of interest, observed during response preparation (correct trials only). Regions showing age- and/or incentive-related effects are italicized.

Talairach Coordinates			Region	BA	Peak F	Volume (ml)
x	y	z				
11	8	-7	***Right Ventral Striatum***	**	4.47	216
2	62	14	Right Superior Frontal Gyrus, medial OFC	10	4.1	270
8	35	-4	Right Anterior Cingulate, VMPFC	24,10	4.04	162
8	14	35	Right Cingulate Gyrus, Dorsal Medial PFC	32,24	9.24	810
11	2	44	***Right Cingulate Gyrus, Dorsal Medial PFC***	24	3.78	189
5	29	32	Right Cingulate Gyrus, Dorsal Medial PFC	32	3.24	108
-7	29	35	Left Medial Frontal Gyrus, Dorsal Medial PFC	8,32	3.63	135
26	-10	44	***Right FEF***	6	5.16	432
35	-4	44	Right FEF	6	4.36	486
23	-10	62	Right FEF	6	4.1	297
29	-10	53	Right FEF	6	3.93	189
17	-10	53	Right FEF	6	3.74	135
-25	-19	47	Left FEF	6	4.9	297
-25	-13	56	***Left FEF***	6	4.59	324
-31	-10	44	Left FEF	6	4.59	270
-22	-1	56	Left FEF	6	4.22	216
-28	-1	35	Left FEF	6	3.52	135
-16	-13	53	Left FEF	6	3.52	189
-40	-4	35	Left FEF	6	3.38	162
-34	8	38	Left FEF	6	3.1	81
5	2	56	***Right SEF***	6	6.28	702
29	-61	35	Right Precuneus	39	7.46	837
8	-58	53	***Right Precuneus***	7	5.81	648
14	-67	56	Right Superior Parietal Lobule	7	4.49	378
-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

Table 4: Regions demonstrating a main effect of time in anatomical regions of interest, observed during saccade response (correct trials only). Regions showing age- and/or incentive-related effects are italicized.

Talairach Coordinates			Region	BA	Peak F	Volume (ml)
x	y	z				
5	38	-7	Right Rectal Gyrus, Medial OFC	10,11	6.84	810
32	32	2	Right Inferior Frontal Gyrus, lateral OFC	47	5.87	567
20	26	-7	Right Inferior Frontal Gyrus, lateral OFC	47	3.01	54
-25	44	-4	Left Middle Frontal Gyrus, lateral OFC	11	4.14	378
-7	38	-13	***Left Rectal Gyrus, Medial OFC***	11,10	3.56	243
2	23	26	Right Cingulate Gyrus, Dorsal Medial PFC	24	6.47	837
-1	11	35	***Left Cingulate Gyrus, Dorsal Medial PFC***	24,32	9.15	891
-4	11	26	Left Cingulate Gyrus, Dorsal Medial PFC	24	7.53	594
-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 FEF	6	15.63	891
41	5	47	Right FEF	6	10.99	864
47	11	35	Right Inferior PCS	6	8.4	864
32	2	32	Right Inferior PCS	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 FEF	6	12.39	864
-22	-13	65	Left FEF	6	8.8	864
-28	-1	44	Left FEF	6	5.67	567
-28	8	53	Left FEF	6	4.54	540
-34	-1	29	Left Inferior PCS	6	4.01	270
2	-10	59	Right SEF	6	8.71	810
-7	-10	62	Left SEF	6	11.02	810
23	-64	50	Right Superior Parietal Lobule	7	12.5	891
14	-67	50	Right Precuneus	7	11.04	783
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 Inferior Parietal Lobule	39	5.92	594
35	-49	44	Right Inferior Parietal Lobule	40, 7	3.98	432
47	-37	41	Right Supramarginal Gyrus	40	4.01	216
-16	-67	47	Left Precuneus	7	16.83	891
-43	-70	38	Left Precuneus	18,39	6.83	567
-16	-76	29	Left Cuneus	18,7	11.58	891
-19	2	8	Left Putamen	**	21.86	891
17	8	2	Right Putamen	**	18.9	891
32	50	32	Right Middle Frontal Gyrus	9	7.38	864
47	26	23	Right Middle Frontal Gyrus	45,46	6.93	891
41	17	26	Right Middle Frontal Gyrus	9,46	6.31	864
32	35	41	Right Middle Frontal Gyrus	8,9	4.24	567
29	41	26	Right Superior Frontal Gyrus	9,10	5.44	702
-43	23	26	Left Middle Frontal Gyrus	9,46	5.64	594
23	56	17	Right Superior Frontal Gyrus	9,10	4.8	675

Table 5: Regions demonstrating age-related effects in anatomical regions of interest, observed during cue (correct trials only).

Talairach Coordinates			Peak F Main effect of Time	Region	BA	Volume (ml)	Omnibus Age or Valence Effects	Effects by Valence Trial Type		
x	y	z						Reward	Punish	Neutral
				Incentive-related Regions						
41	40	-2	4.35	Right Inferior Frontal Gyrus	10, 47	486	Time X Age		Time X Age	
				Oculomotor / Inhibitory Control Regions						
44	-5	46	12.69	Right Middle Frontal Gyrus (FEF)	6	891	Age			Age
32	-11	43	9.89	Right Middle Frontal Gyrus (FEF)	6	837	Valence; Valence X Age; Valence X Time X Age	Time X Age	Age	
-1	4	46	11.18	Left Medial Frontal Gyrus (SEF)	6	891	Age; Valence X Age	Time X Age	Age	
-28	-62	40	12.18	Left Superior Parietal Lobule	39, 7	891	Valence; Age; Valence X Time		Age	

Table 6: Regions demonstrating age-related effects in anatomical regions of interest, observed during response preparation (correct trials only).

Talairach Coordinates			Peak F Main effect of Time	Region	BA	Volume (ml)	Omnibus Age or Valence Effects	Effects by Valence Trial Type		
x	y	z						Reward	Punish	Neutral
				Incentive-related Regions						
-37	31	-5	4.95	Left Inferior Frontal Gyrus	47, 11	324	Valence X Time; Valence X Time X Age	Time X Age	Time X Age	
26	46	-5	4.63	Right Middle Orbital Gyrus	10, 11	324	Valence X Time X Age	Time X Age	Time X Age	
8	22	22	7.85	Right Anterior Cingulate (DMPFC)	24, 32	756	Valence X Time; Valence X Time X Age	Time X Age	Time X Age	
				Oculomotor / Inhibitory Control Regions						
44	1	34	6.96	Right Inferior Precentral Sulcus	6, 9	891	Valence; Age; Valence X Time; Valence X Time X Age	Time X Age	Age	
8	4	49	3.56	Right Medial Frontal Gyrus (SEF)	6	594	Valence; Age; Valence X Time X Age	Time X Age	Age	
-25	-59	40	6.99	Left Superior Parietal Lobule	7	837	Valence; Age			Time X Age
5	-62	52	8.39	Right Precuneus	7	864	Valence X Time X Age	Time X Age		
-1	-56	43	10.29	Left Precuneus	7	891	Valence; Valence X	Time X	Time X	

							Time; Valence X Time X Age	Age	Age
20	-62	34	4.85	Right Superior Occipital Gyrus	7, 31	675	Valence; Valence X Time; Valence X Time X Age	Time X Age	

Table 7: Regions demonstrating age-related effects in anatomical regions of interest, observed during saccade response (correct trials only).

Talairach Coordinates			Peak F Main effect of Time	Region	BA	Volume (ml)	Omnibus Age or Valence Effects	Effects by Valence Trial Type		
x	y	z						Reward	Punish	Neutral
				Incentive-related Regions						
-13	16	-2	8.71	Left Ventral Striatum	-	891	Age	Age		
-7	31	22	6.28	Left Anterior Cingulate (DMPFC)	32, 24	756	Time X Age			Time X Age
-25	-2	-14	12.20	Left Amygdala	-	783	Age; Time X Age		Age; Time X Age	Time X Age
29	-8	-14	11.91	Right Amygdala	-	837	Time X Age	Age; Time X Age		Time X Age
				Oculomotor / Inhibitory Control Regions						
41	-11	46	34.62	Right Middle Frontal Gyrus (FEF)	6	891	Valence; Valence X Time X Age	Age		
20	-8	55	17.99	Right Middle Frontal Gyrus (FEF)	6	891	Valence X Time X Age	Time X Age	Time X Age	
-34	-8	46	30.10	Left Middle Frontal Gyrus (FEF)	6	891	Valence; Valence X Time X Age	Time X Age		
-4	-8	55	30.60	Left Medial Frontal Gyrus (SEF)	6	891	Time X Age; Valence X Time; Valence X Time	Time X Age	Time X Age	

							X Age			
20	-62	49	35.61	Right Superior Parietal Lobule	7	891	Age; Valence X Time; Valence X Time X Age	Time X Age		
26	-47	43	16.88	Right Inferior Parietal Lobule	7	891	Age		Age	
2	-20	4	23.79	Right Thalamus	-	891	Time X Age	Time X Age		
11	-14	4	20.81	Right Thalamus	-	891	Time X Age			Time X Age

Table 8: Regions demonstrating only valence-related effects in anatomical regions of interest, observed during cue (correct trials only).

Talairach Coordinates			Peak F Main effect of Time	Region	BA	Volume (ml)	Omnibus Time or Valence Effects	Valence		Valence by Time	
x	y	z						F	*p*	F	*p*
				Incentive-related Regions							
5	10	-8	5.03	Right Ventral Striatum (Nucleus Accumbens)	-	756	Valence; Valence X Time	8.1	0.001	3.0	0.001
-7	7	-14	5.07	Left Ventral Striatum	-	567					
32	25	-2	6.33	Right Inferior Frontal Gyrus	47	675					
-28	31	-11	7.66	Left Inferior Frontal Gyrus	47, 11	729					
8	16	31	4.87	Right Cingulate Gyrus (DMPFC)	32, 24	594	Valence X Time			3.3	0.001
8	22	40	5.05	Right Cingulate Gyrus (DMPFC)	32	486					
-4	52	-2	11.75	Left Medial Frontal Gyrus	10, 32	891	Valence X Time			1.8	0.01
-4	37	1	8.56	Left Anterior Cingulate (VMPFC)	24, 32	864					
-4	31	16	5.27	Left Anterior Cingulate (VMPFC)	24, 32	837	Valence; Valence X Time	8.1	0.001	1.9	0.007
-7	16	28	4.04	Left Cingulate Gyrus (DMPFC)	24, 32	324	Valence	12.7	0.001		
23	-20	-8	9.83	Right Parahippocampal Gyrus	28	513	Valence X Time			2.2	0.001

-13	-8	-11	4.37	Left Parahippocampal Gyrus/Left Amygdala	28, 34	135					
-22	-23	-8	11.31	Left Parahippocampal Gyrus	28	486	Valence; Valence X Time	7.6	0.001	2.9	0.001
				Oculomotor / Inhibitory Control Regions							
-31	-8	40	10.91	Left Middle Frontal Gyrus (FEF)	6	864					
38	-2	34	10.86	Right Inferior Precentral Sulcus	6, 9	864					
-40	-2	31	12.38	Left Inferior Precentral Sulcus	6, 9	864	Valence; Valence X Time	4.6	0.014	2.1	0.002
32	-62	43	12.85	Right Superior Parietal Lobule	7	891	Valence X Time			3.9	0.001
5	-80	34	11.49	Right Cuneus	19, 7	891					
38	-56	37	11.21	Right Angular Gyrus	40	837					
-46	-41	40	5.80	Left Inferior Parietal Lobule	40	621					
-4	-50	34	5.26	Left Precuneus	7, 31	621					
-25	10	-2	5.58	Left Putamen	-	378					
5	-20	7	5.18	Right Thalamus	-	540					
5	7	13	4.83	Right Caudate	-	351					
44	25	19	7.87	Right Middle Frontal Gyrus	46	837	Valence; Valence X Time	5.0	0.01	1.5	0.05
-4	55	22	3.50	Left Superior Frontal Gyrus	9, 10	324					

Table 9: Regions demonstrating only valence-related effects in anatomical regions of interest, observed during response preparation (correct trials only).

Talairach Coordinates			Peak F Main effect of Time	Region	BA	Volume (ml)	Omnibus Time or Valence Effects	Valence		Valence by Time	
x	y	z						F	*p*	F	*p*
				Incentive-related Regions							
11	7	1	7.54	Right Ventral Striatum	-	837					
-7	7	-2	6.14	Left Ventral Striatum	-	594					
35	22	-2	10.17	Right Inferior Frontal Gyrus	13, 47	891	Valence; Valence X Time	2.1	0.001	3.2	0.016
44	16	-2	11.88	Right Inferior Frontal Gyrus	13, 47	891	Valence; Valence X Time	20.3	0.001	2.0	0.003
5	40	10	9.01	Right Anterior Cingulate (DMPFC)	32, 24	891					
-1	34	16	8.69	Left Anterior Cingulate (DMPFC)	24, 32	864					
-10	25	19	8.47	Left Anterior Cingulate (DMPFC)	32, 24	729	Valence X Time			2.1	0.001
2	19	31	8.86	Right Cingulate Gyrus	32, 24	891					
-7	49	7	5.21	Left Medial Frontal Gyrus	10, 32	648	Valence X Time			2.0	0.003
				Oculomotor / Inhibitory Control Regions							
32	4	40	6.44	Right Middle Frontal	6	621	Valence	8.8	0.001		

				Gyrus (FEF)							
-25	-8	43	5.25	Left Middle Frontal Gyrus (FEF)	6	567	Valence; Valence X Time	6.1	0.004	1.6	0.03
32	13	43	5.14	Right Middle Frontal Gyrus	6, 8	540	Valence	4.8	0.012		
29	-62	46	5.73	Right Superior Parietal Lobule	7	783					
47	-44	46	5.72	Right Inferior Parietal Lobule	40	702					
-34	-50	49	4.64	Left Inferior Parietal Lobule	7, 40	702	Valence	5.5	0.014		
-34	-35	37	5.00	Left Inferior Parietal Lobule	40	729	Valence	7.3	0.007		
11	-5	19	7.59	Right Caudate	-	810					
-7	1	7	4.92	Left Caudate	-	648	Valence; Valence X Time	7.1	0.002		
14	-5	13	7.94	Right Thalamus	-	621					
-13	-11	13	4.95	Left Thalamus	-	594					
41	52	1	6.24	Right Middle Frontal Gyrus	10	810	Valence	3.2	0.05		
-28	25	31	6.38	Left Middle Frontal Gyrus	9	675					
5	46	31	5.97	Right Medial Frontal Gyrus	9	702					
-22	37	31	4.96	Left Superior Frontal Gyrus	9	567	Valence	3.8	0.04		
44	40	4	4.36	Right Inferior Frontal Gyrus	46, 10	513	Valence; Valence X Time	5.7	0.006	2.8	0.001

Table 10: Regions demonstrating valence-related effects in anatomical regions of interest, observed during saccade response (correct trials only).

Talairach Coordinates			Peak F Main effect of Time	Region	BA	Volume (ml)	Omnibus Time or Valence Effects	Valence		Valence by Time	
x	y	z						F	*p*	F	*p*
				Incentive-related Regions							
32	19	-14	12.33	Right Inferior Frontal Gyrus	47, 13	864					
44	28	1	4.49	Right Inferior Frontal Gyrus	47	702	Valence X Time			2.3	0.001
-28	16	-11	7.66	Left Inferior Frontal Gyrus	47, 13	783					
-4	4	40	21.14	Left Cingulate Gyrus (dmPFC)	24, 32	891					
8	16	25	12.55	Right Anterior Cingulate (dmPFC)	24, 32	864	Valence X Time			2.0	0.003
2	43	10	11.27	Right Anterior Cingulate (vmPFC)	32, 10	864					
8	28	22	8.98	Right Anterior Cingulate (dmPFC)	32, 24	810					
-10	16	28	11.32	Left Anterior Cingulate (dmPFC)	24, 32	729					
				Oculomotor / Inhibitory Control Regions							

-22	-11	46	34.72	Left Middle Frontal Gyrus (FEF)	6	891					
41	-2	28	8.54	Right Inferior Precentral Sulcus	9, 6	783	Valence; Valence X Time	3.5	0.037	2.2	0.001
-19	-59	49	27.71	Left Superior Parietal Lobule	7	891					
5	-2	7	22.74	Right Caudate	-	891					
14	16	4	10.78	Right Caudate	-	837	Valence X Time			2.2	0.046
17	7	19	11.92	Right Caudate	-	891					
-10	-2	10	23.60	Left Caudate	-	891					
11	-23	10	21.77	Right Thalamus	-	891					
-7	-17	4	20.77	Left Thalamus	-	837					
-16	-20	10	19.80	Left Thalamus	-	891	Valence X Time			1.7	0.016
-19	1	7	12.84	Left Putamen	-	837					
26	31	22	10.55	Right Middle Frontal Gyrus	9	864					
32	37	10	6.34	Right Middle Frontal Gyrus	10, 46	729					
-37	37	28	5.56	Left Middle Frontal Gyrus	9	729					
-31	28	31	4.61	Left Middle Frontal Gyrus	9	567	Valence X Time			1.9	0.005

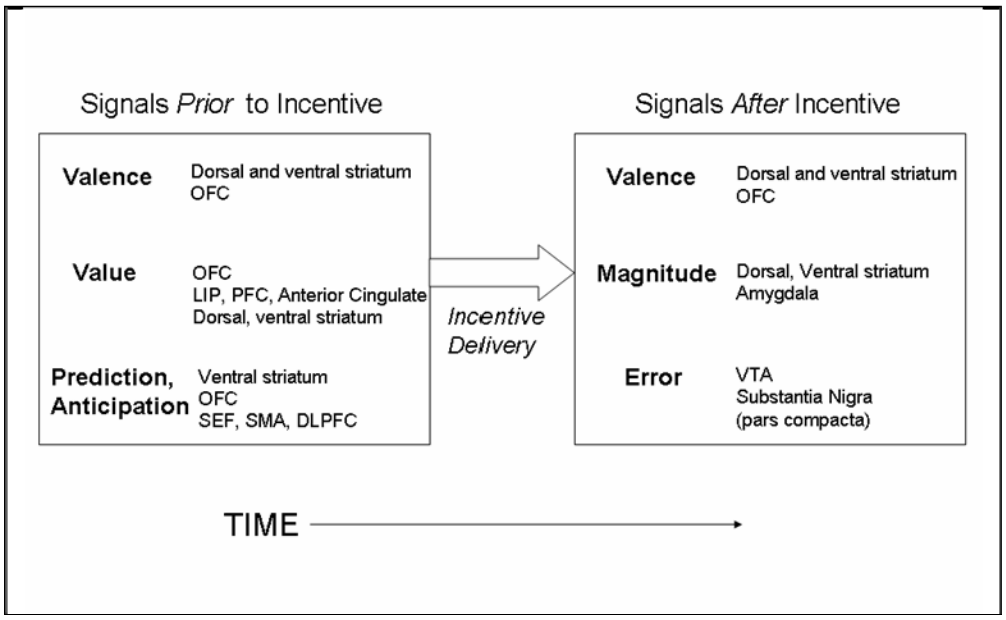

Figure 1. Examples of dissociable incentive-related 'signals' and contributing brain regions.

Incentive signals can be broadly categorized as those occurring prior to (e.g., reward detection, value estimation; 'anticipatory processing') and after (e.g., prediction error signals; 'consummatory processing') incentive delivery.

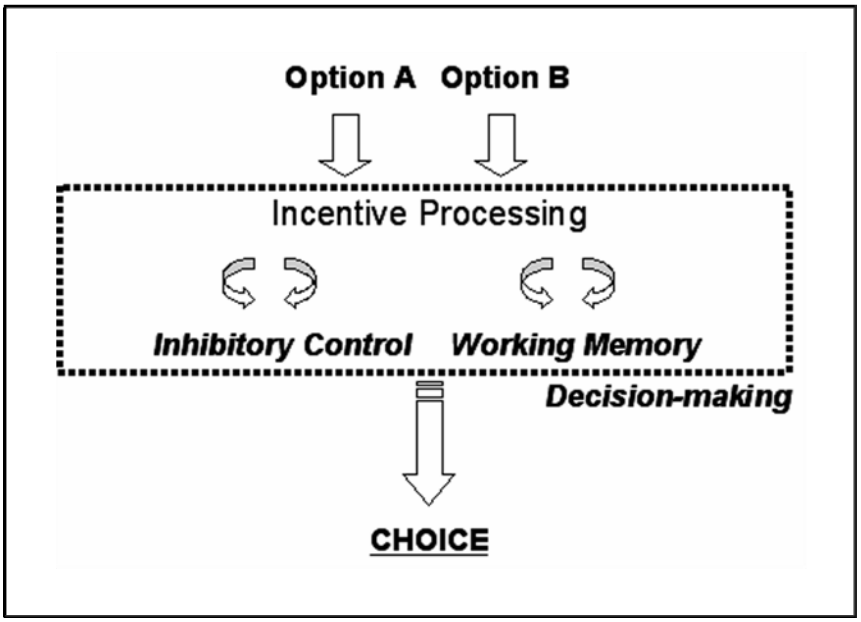

Figure 2. A simple model emphasizing the interaction between incentive processing and basic cognitive control abilities in decision-making.

Suboptimal decision-making has been suggested to contribute to risk-taking behavior. Immaturities in brain systems supporting how incentives are represented in the brain, as well as immaturities in specific cognitive control systems like working memory and response inhibition, are proposed to contribute to poor decision-making.

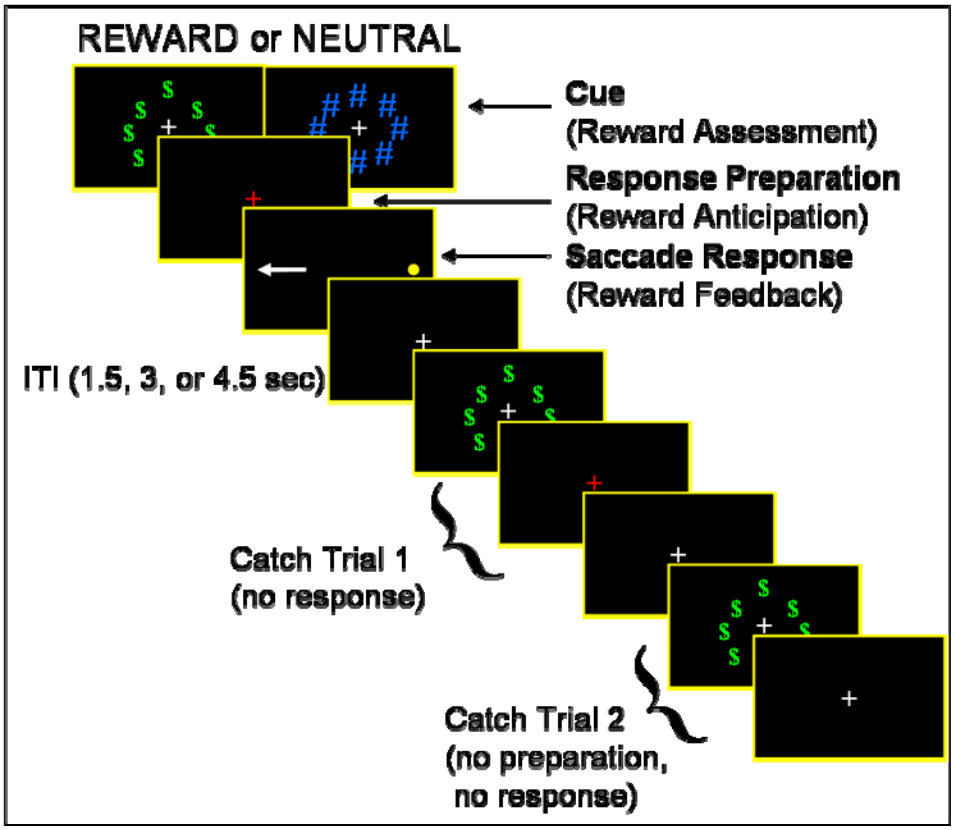

Figure 3. Depiction of the rewarded antisaccade (fMRI) task.

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 1.5sec. Following the cue, the fixation cross turned red to indicate the response preparation period (1.5). Finally, a peripheral light appeared for the first 75msec of a 1.5sec 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 sec) between all trials.

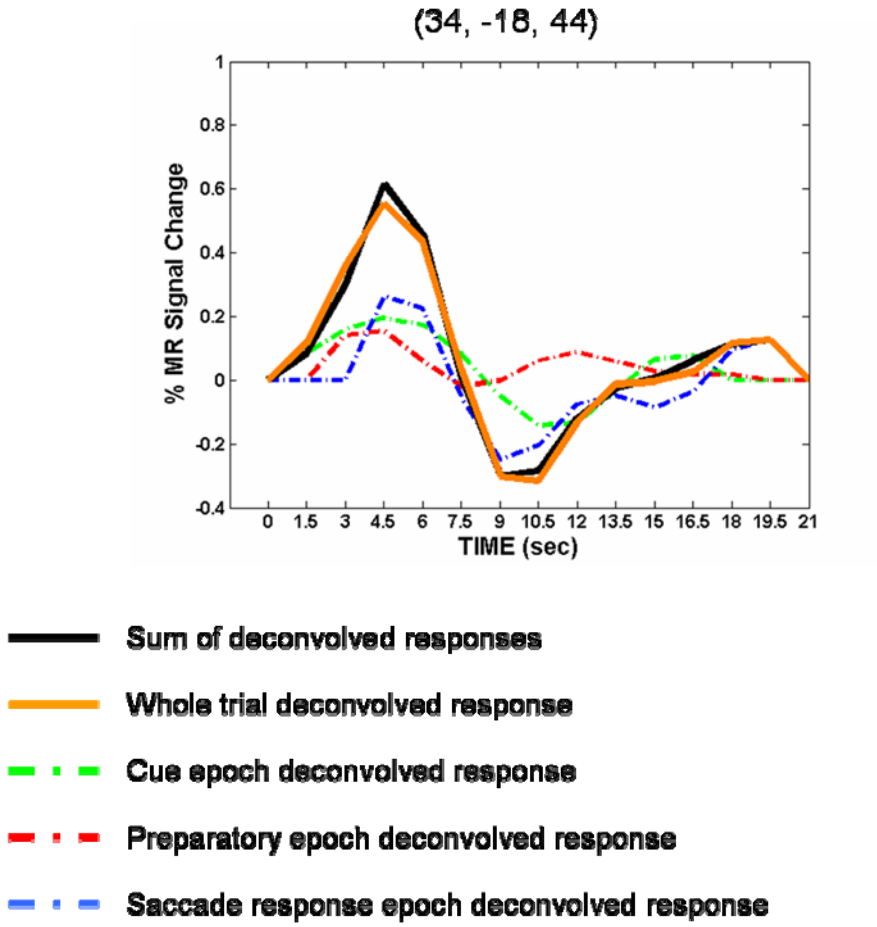

Figure 4. Reliability check for deconvolution: the sum of estimated time courses from trial epochs is equivalent to whole trial estimates.

Time courses were obtained from the same voxel (Talairach coordinates: 34, -18, 44; precentral gyrus) in a representative adult subject. Dash-dot lines are the time course estimates from separate trial epochs (green = cue; red = response preparation; blue = saccade response). Black line shows the point-by-point sum of the time courses from the three trial epochs. Response preparation time course has been shifted by 1.5 seconds and saccade response time course has been shifted by 3 seconds to reflect when these events would occur in a typical trial. Orange line shows the estimated response from a separate deconvolution model in which the response to the whole trial was estimated by coding just the start of the trial.

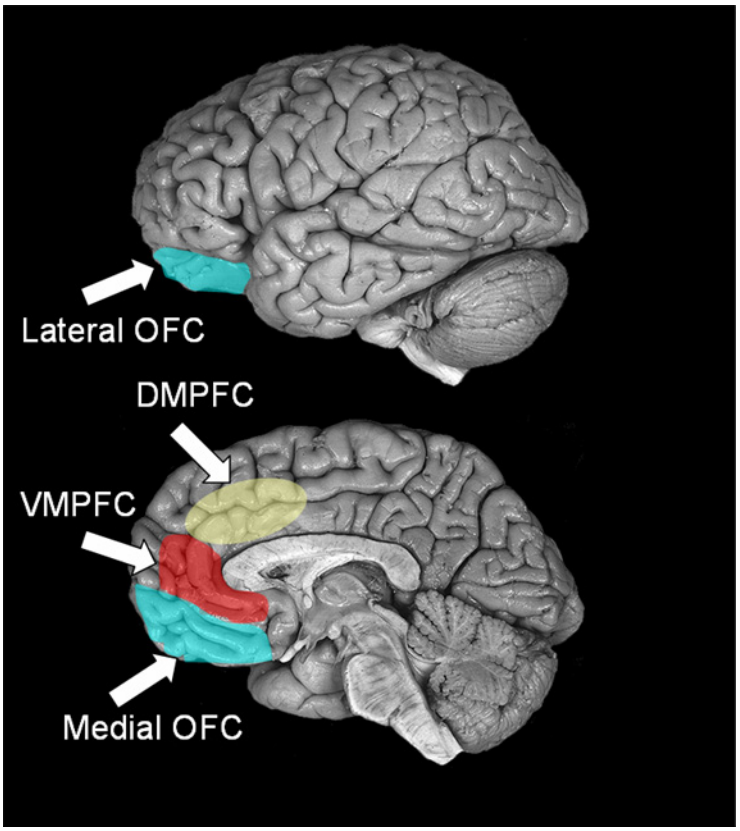

Figure 5.The approximate locations of reward-related anatomical ROI within medial prefrontal cortical regions, superimposed on the lateral (top) and medial (bottom) surface of the right hemisphere.

Abbreviations: DMPFC = dorsal medial prefrontal cortex (shown here in yellow); OFC = orbitofrontal cortex (shown here in blue); VMPFC = ventral medial prefrontal cortex (shown here in red). Brain images used for underlay were obtained with permission from the Digital Anatomist: Interactive Brain Atlas: http://sig.biostr.washington.edu/projects/da/

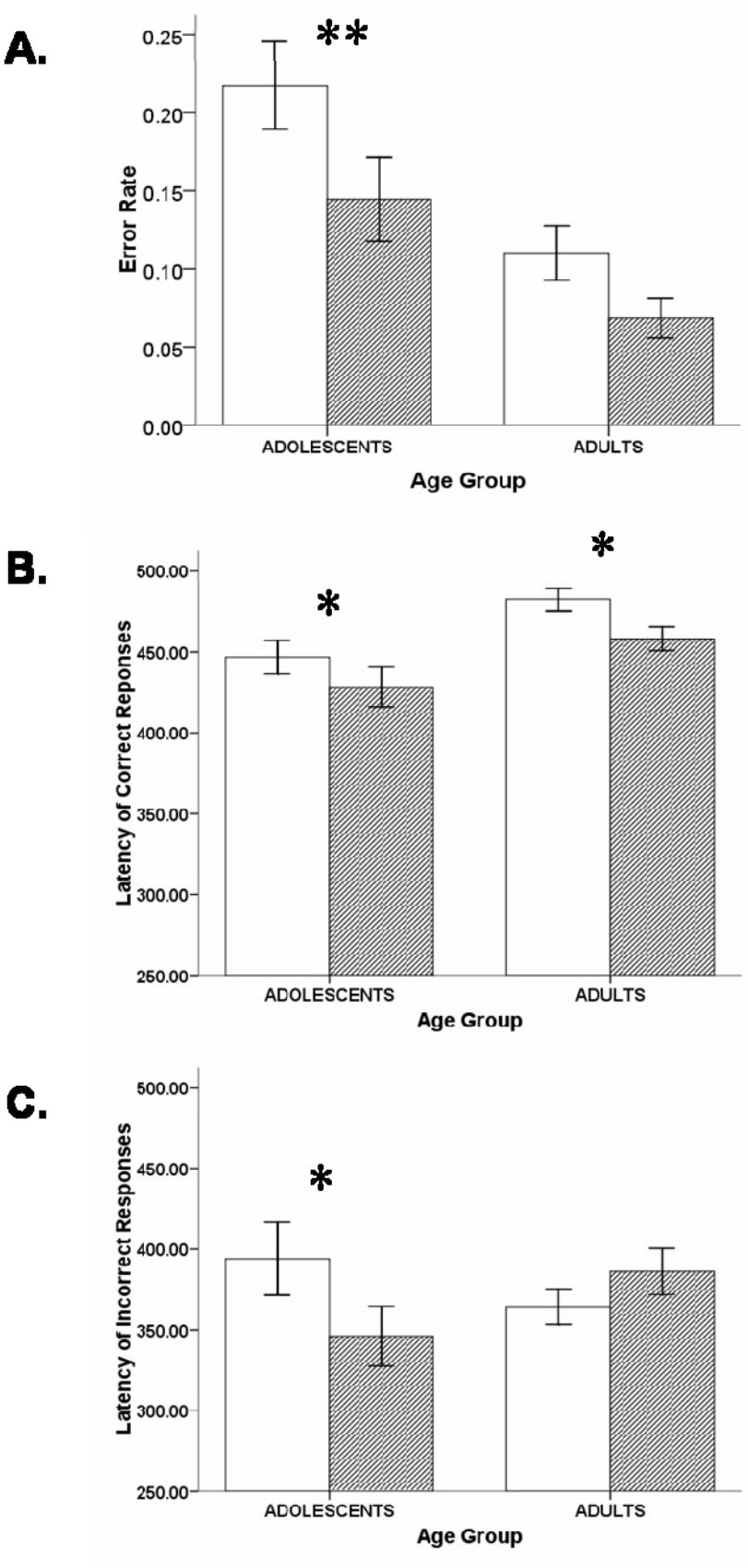

Figure 6. Results of eye data obtained during imaging.

A. Error rate for adolescents (left bars) and adults (right bars) for neutral (white bars) and rewarded (hashed bars) trials. B. Latencies of correct antisaccades. C. Latencies of inhibitory errors. Single asterisk (*) indicates significance at .05 alpha level, double asterisk (**) indicates significance at 0.001 alpha level. Error bars represent +/- 1 standard error of the mean.

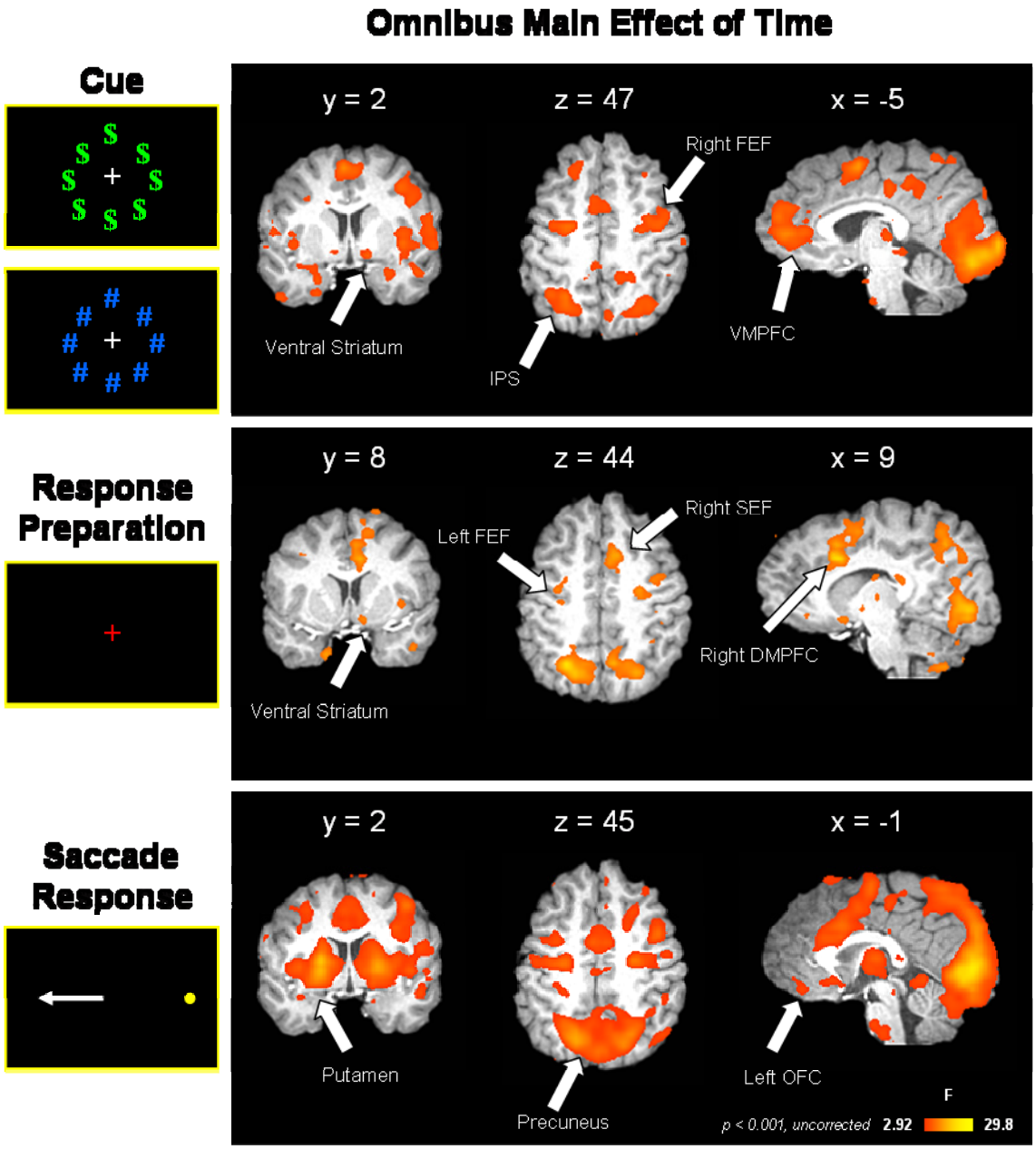

Figure 7. Main effect of time maps for cue, response preparation, and saccade response epochs, collapsed across incentive type and age group.

Image threshold is set at p<0.001 (uncorrected). Right side of image = right brain. Abbreviations: FEF = frontal eye field; DMPFC = dorsal medial prefrontal cortex; IPS = intraparietal sulcus; OFC = orbitofrontal cortex; SEF = supplementary eye field; VMPFC = ventral medial prefrontal cortex.

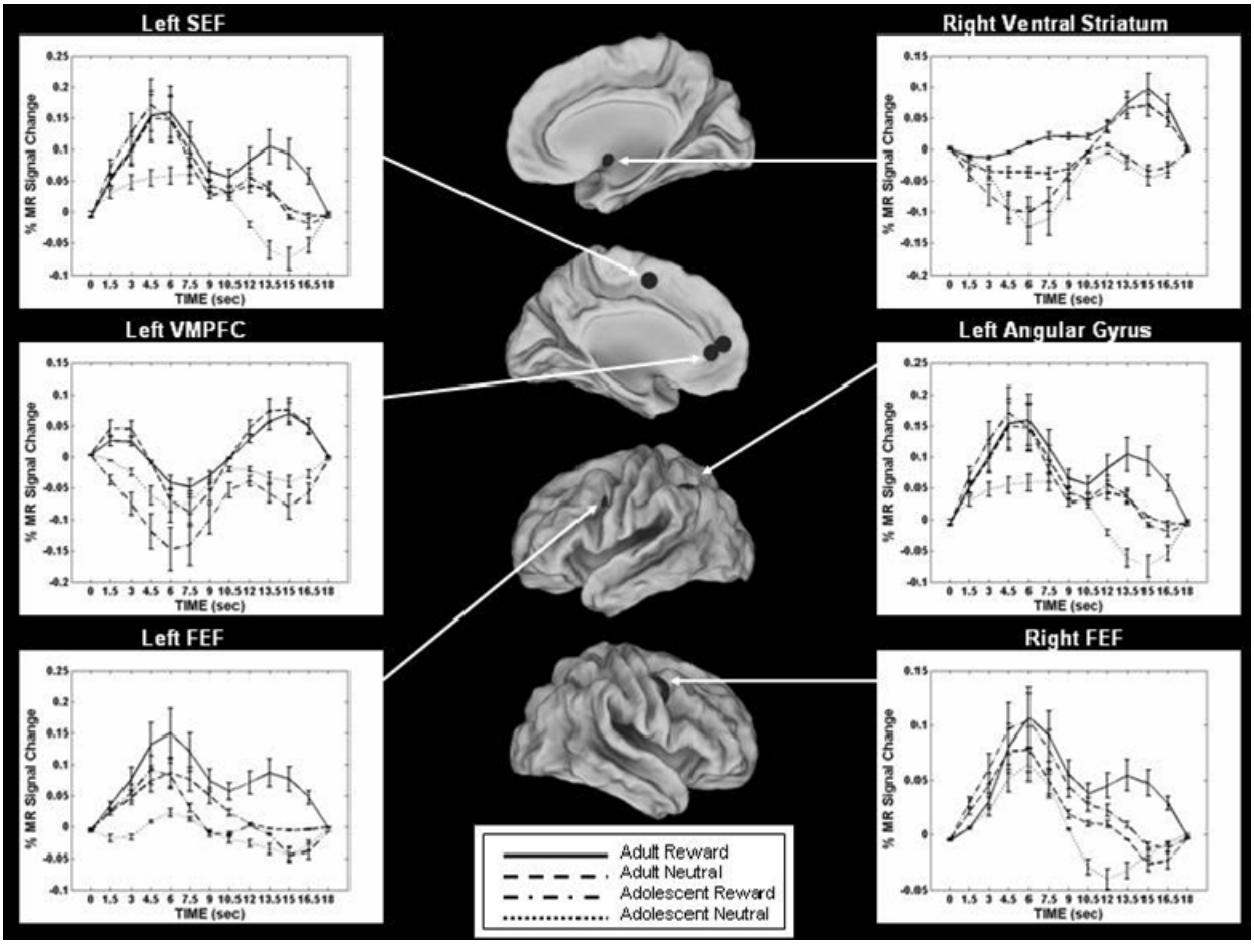

Figure 8. Cue epoch time courses showing age and/or developmental effects.

Time courses were extracted from mask region shown in black (indicated by white arrow), projected onto Human PALS atlas using Caret (version 5.51). As indicated in legend, solid line = adult response during reward trials; dashed line = adult response during neutral trials; dash-dot line= adolescent response to reward trials, dotted line = adolescent response to neutral trials. Error bars represent +/- 1 standard error of the mean at each time point. Abbreviations: FEF = frontal eye field; SEF = supplementary eye field; VMPFC = ventral medial prefrontal cortex. Note that while two VMPFC clusters are shown, only one set of time courses is displayed given that both clusters demonstrated equivalent patterns.

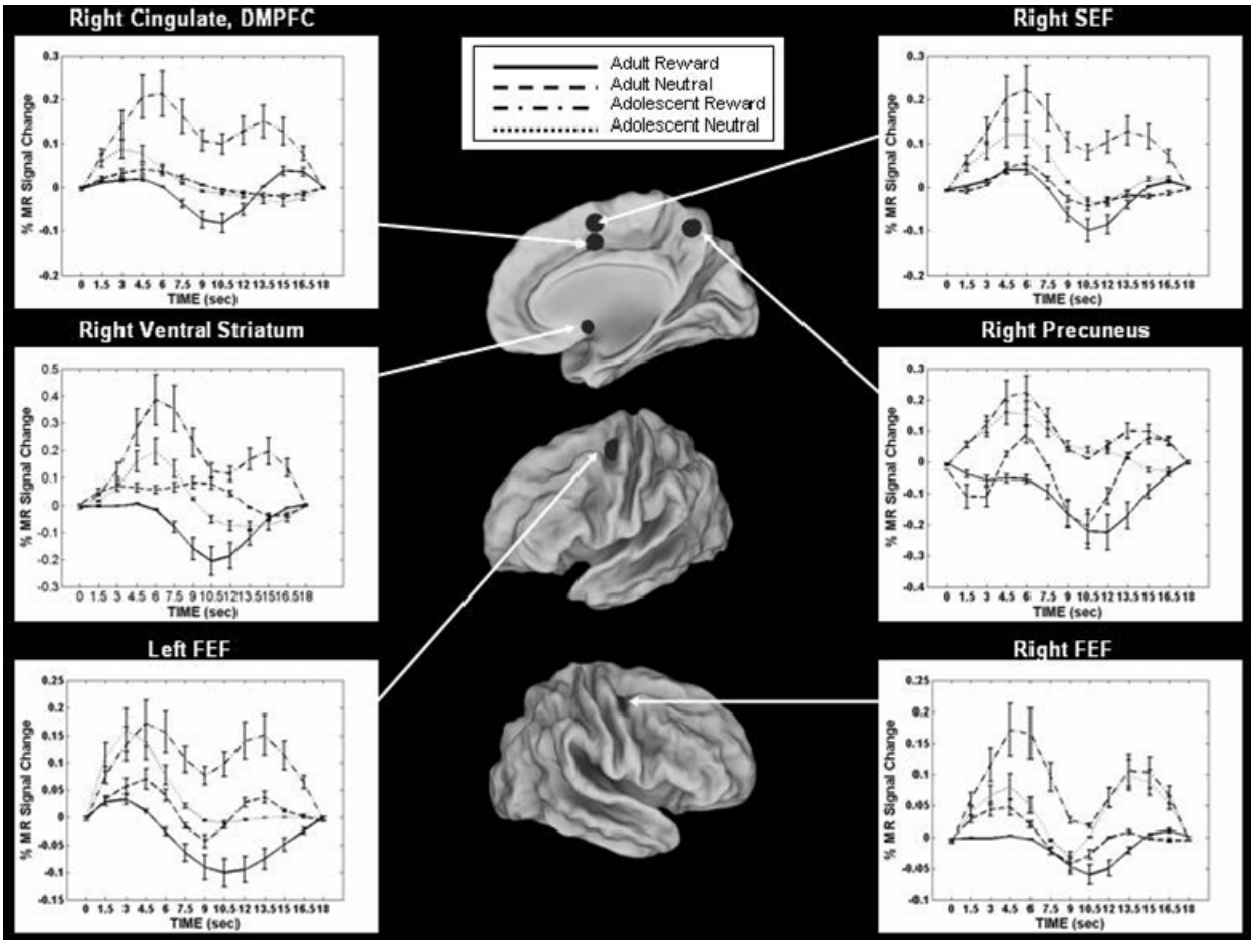

Figure 9. Response preparation epoch time courses showing age and/or developmental effects.

Time courses were extracted from mask region (black spheres indicated by white arrow), projected onto Human PALS atlas using Caret (version 5.51). Middle and bottom cortical surfaces are tilted from standard views to better show regions of interest. As indicated in legend, solid line = adult response during reward trials; dashed line = adult response during neutral trials; dash-dot line= adolescent response to reward trials, dotted line = adolescent response to neutral trials. Error bars represent +/- 1 standard error of the mean at each time point. Abbreviations: DMPFC = dorsal medial prefrontal cortex; FEF = frontal eye field; SEF = supplementary eye field.

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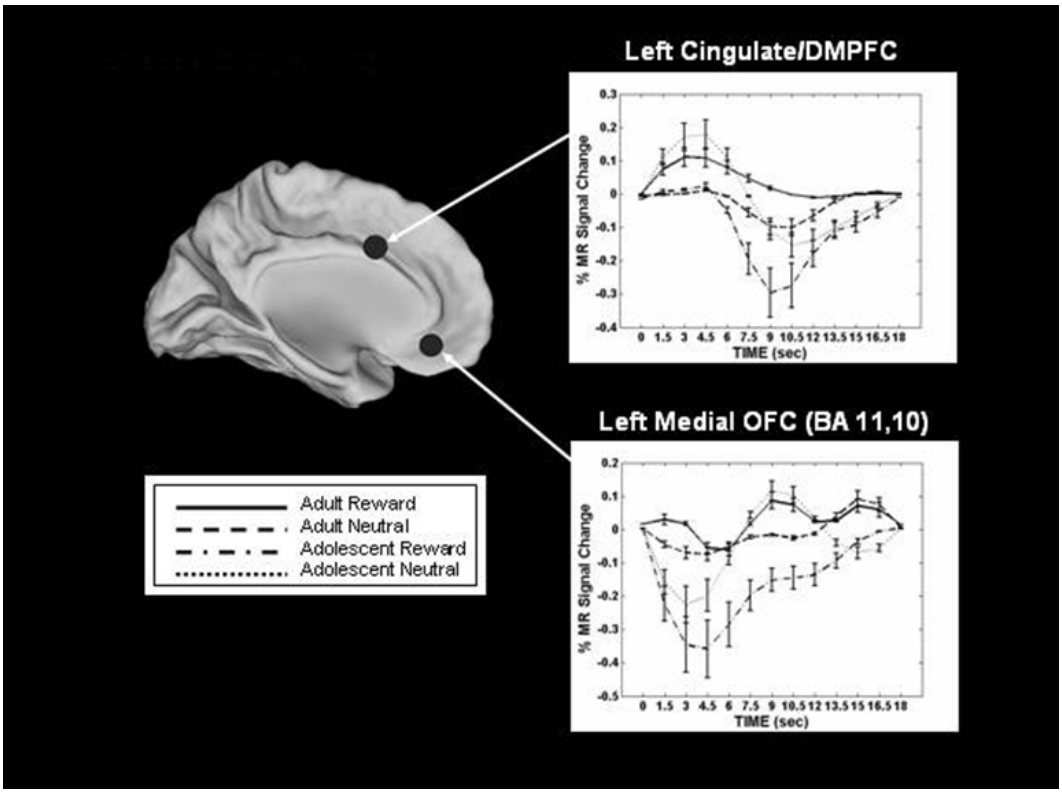

Figure 10. Saccade response epoch time courses showing age and/or developmental effects.

Time courses were extracted from mask region shown in black (indicated by white arrow), projected onto Human PALS atlas using Caret (version 5.51). As indicated in legend, solid line = adult response during reward trials; dashed line = adult response during neutral trials; dash-dot line= adolescent response to reward trials, dotted line = adolescent response to neutral trials. Error bars represent +/- 1 standard error of the mean at each time point.

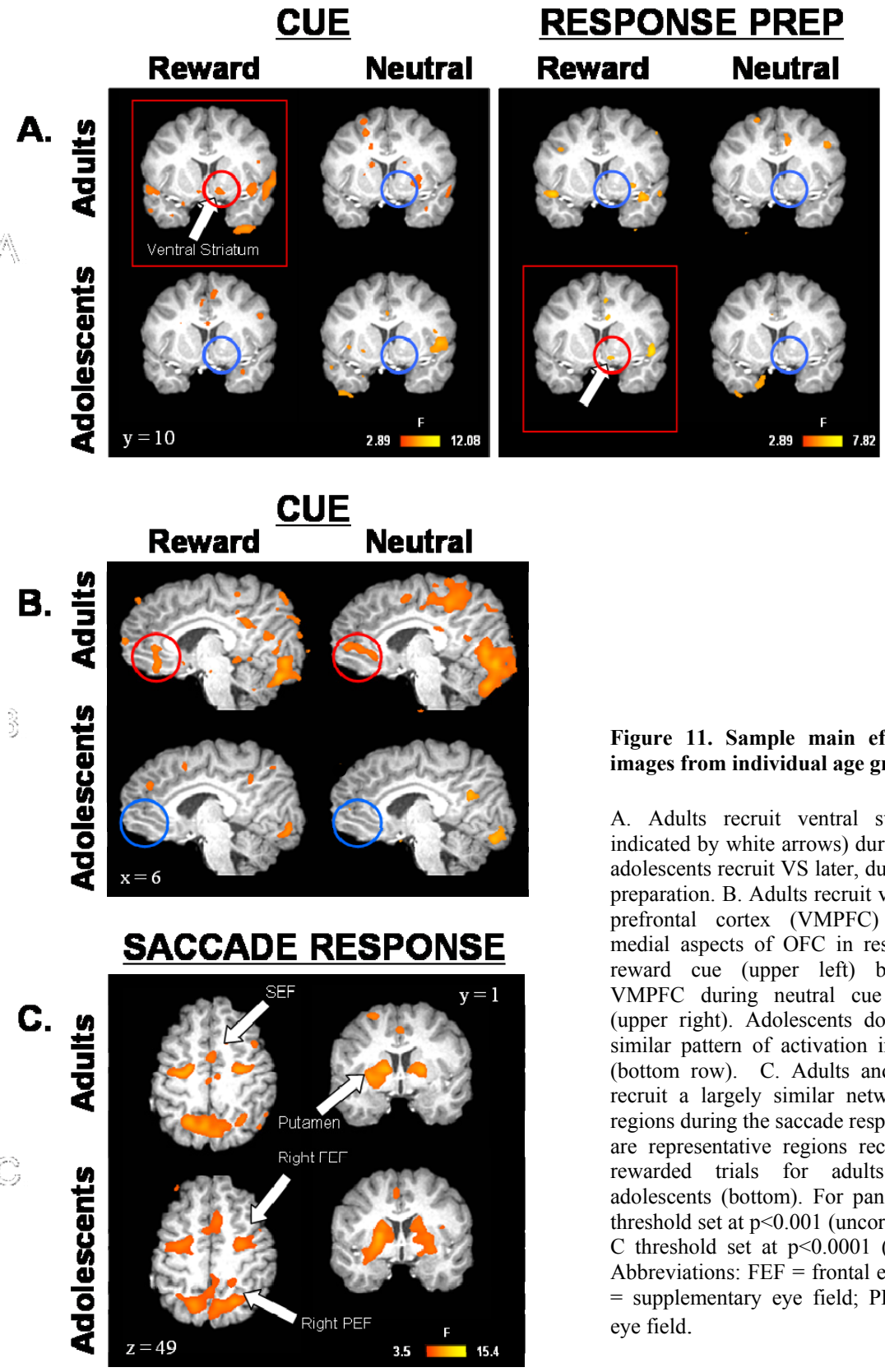

Figure 11. Sample main effect of time images from individual age groups.

A. Adults recruit ventral striatum (VS; indicated by white arrows) during cue while adolescents recruit VS later, during response preparation. B. Adults recruit ventral medial prefrontal cortex (VMPFC) along with medial aspects of OFC in response to the reward cue (upper left) but primarily VMPFC during neutral cue presentation (upper right). Adolescents do not show a similar pattern of activation in these areas (bottom row). C. Adults and adolescents recruit a largely similar network of brain regions during the saccade response – shown are representative regions recruited during rewarded trials for adults (top) and adolescents (bottom). For panels A and B, threshold set at $p<0.001$ (uncorrected), panel C threshold set at $p<0.0001$ (uncorrected). Abbreviations: FEF = frontal eye field; SEF = supplementary eye field; PEF = parietal eye field.

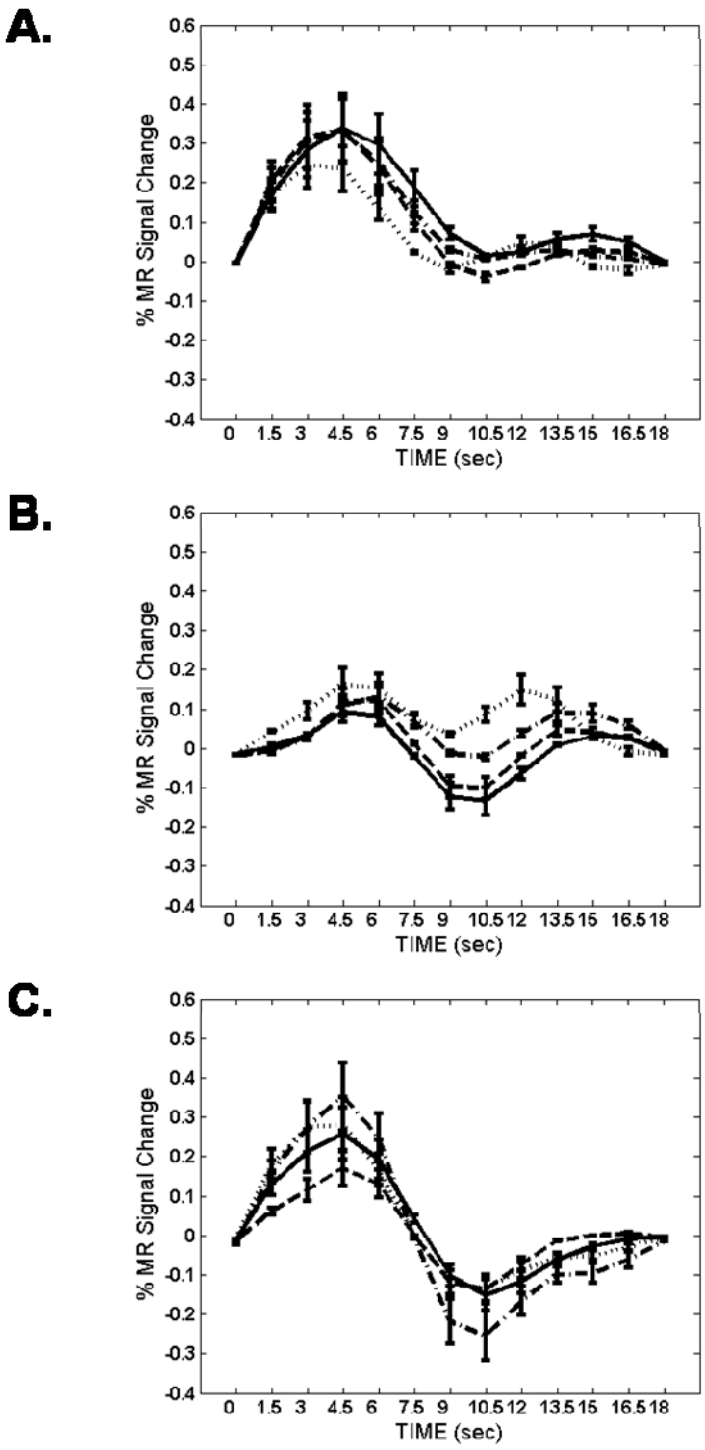

Figure 12. Mean time courses from regions in visual cortex (BA 17/18) observed during (A) cue, (B) response preparation, and (C) saccade response.

Adult reward trial response = solid line; adult neutral = dashed line; adolescent reward = dash-dot line; adolescent neutral = dotted line. Error bars represent +/-1 standard error of the mean at each point. Talairach coordinates for peak voxel of each cluster: Cue (-17, -95, 6); Preparation (-5, -76, -1); Saccade (-5, -80, -1).

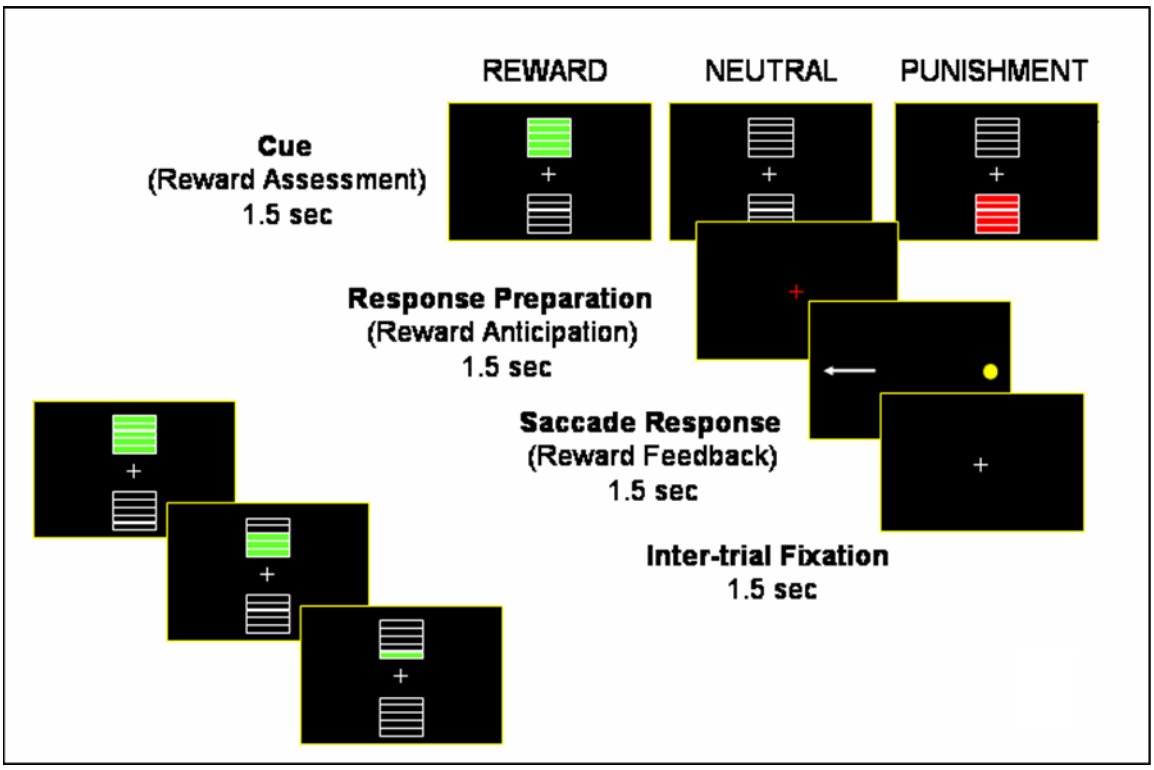

Figure 13. 'Bars' antisaccade (behavioral) task design.

Subjects first viewed an incentive-indicating cue for 1.5 seconds. Reward trials were indicated by 1 to 5 green bars (shown at bottom left) above the central fixation, punishment trials were indicated by 1-5 red bars below the central fixation (not shown), and neutral trials were indicated by empty bars above and below the central fixation. The number of points at stake on each trial was indicated by the number of filled bars. Subjects next viewed a red fixation cross (1.5sec), indicating that they should prepare to generate a response. A peripheral stimulus then briefly appeared and subjects had 1.5 seconds to respond. Each trial concluded with a 1.5 second inter-trial fixation period.

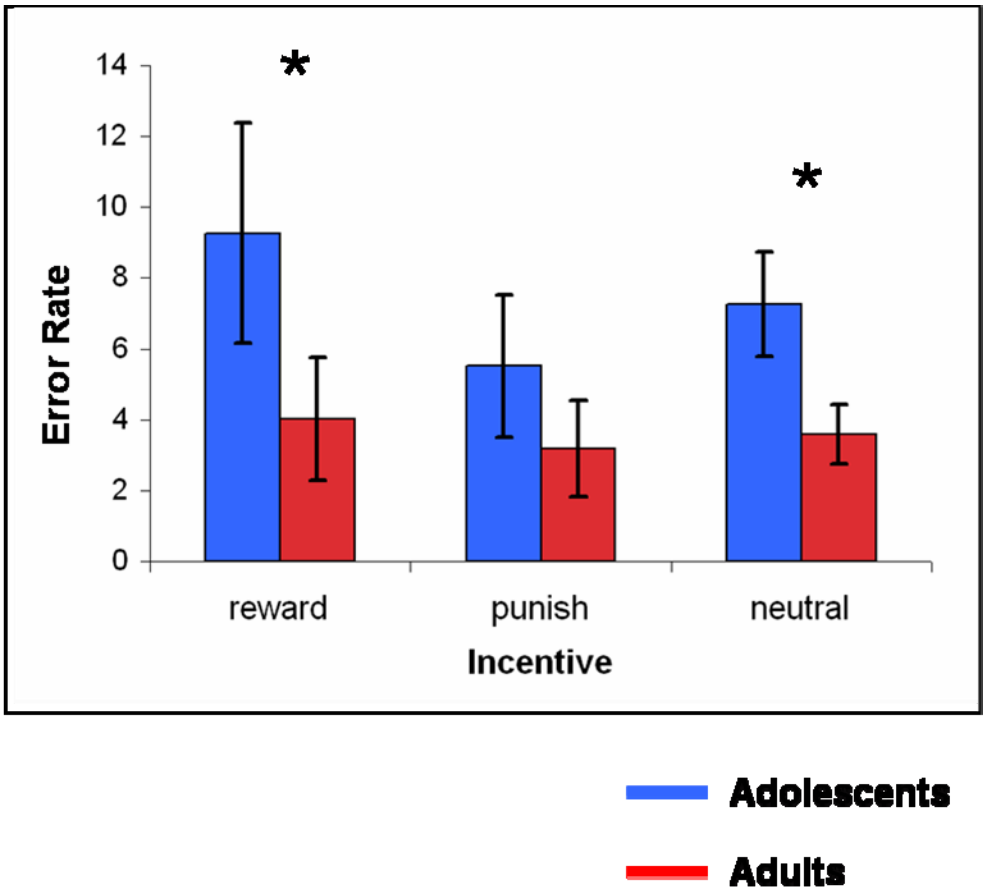

Figure 14. Behavioral eye data results collapsed across incentive magnitudes.

Blue bars = adolescents, red bars = adults. Asterisks denote significant ($p<0.05$) differences. Error bars represent +/- 1 standard error of the mean.

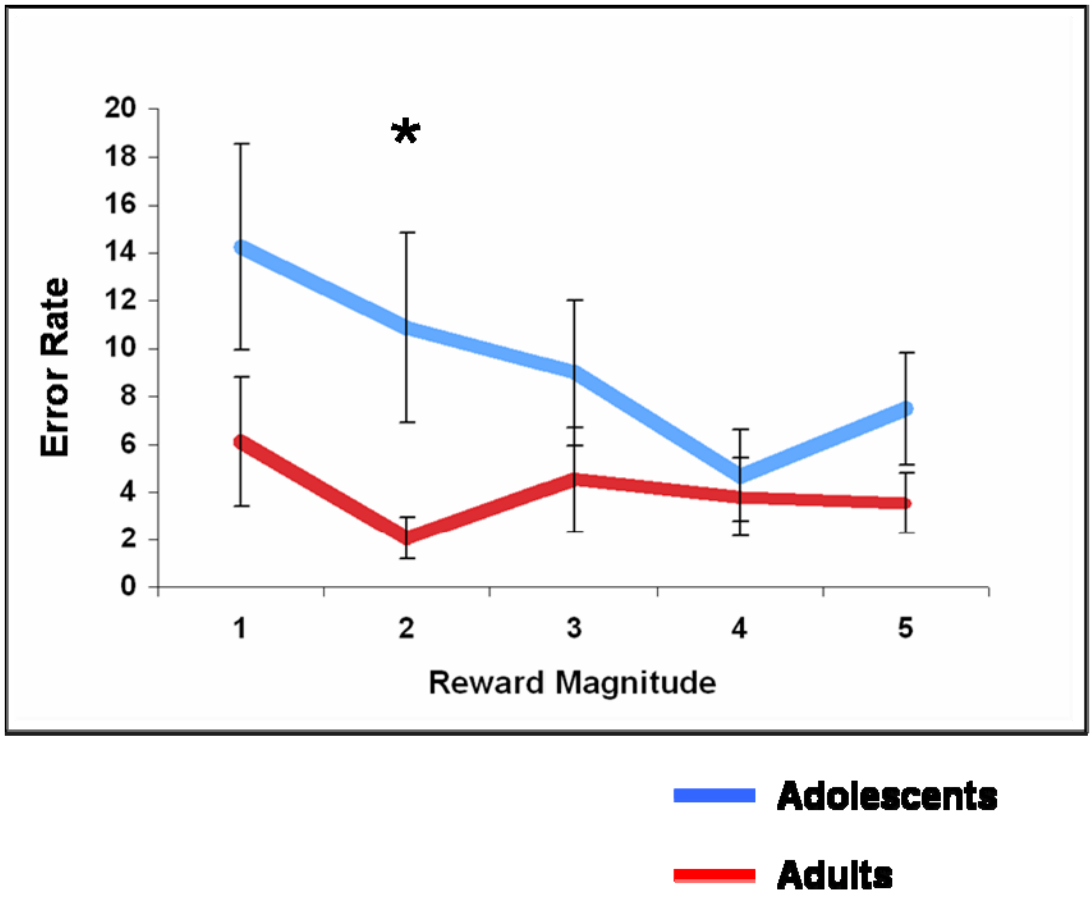

Figure 15. Error rates at each reward magnitude.

Blue line = adolescents, red line = adults. Asterisk denotes significant ($p<0.05$) difference. Error bars represent +/- 1 standard error of the mean.

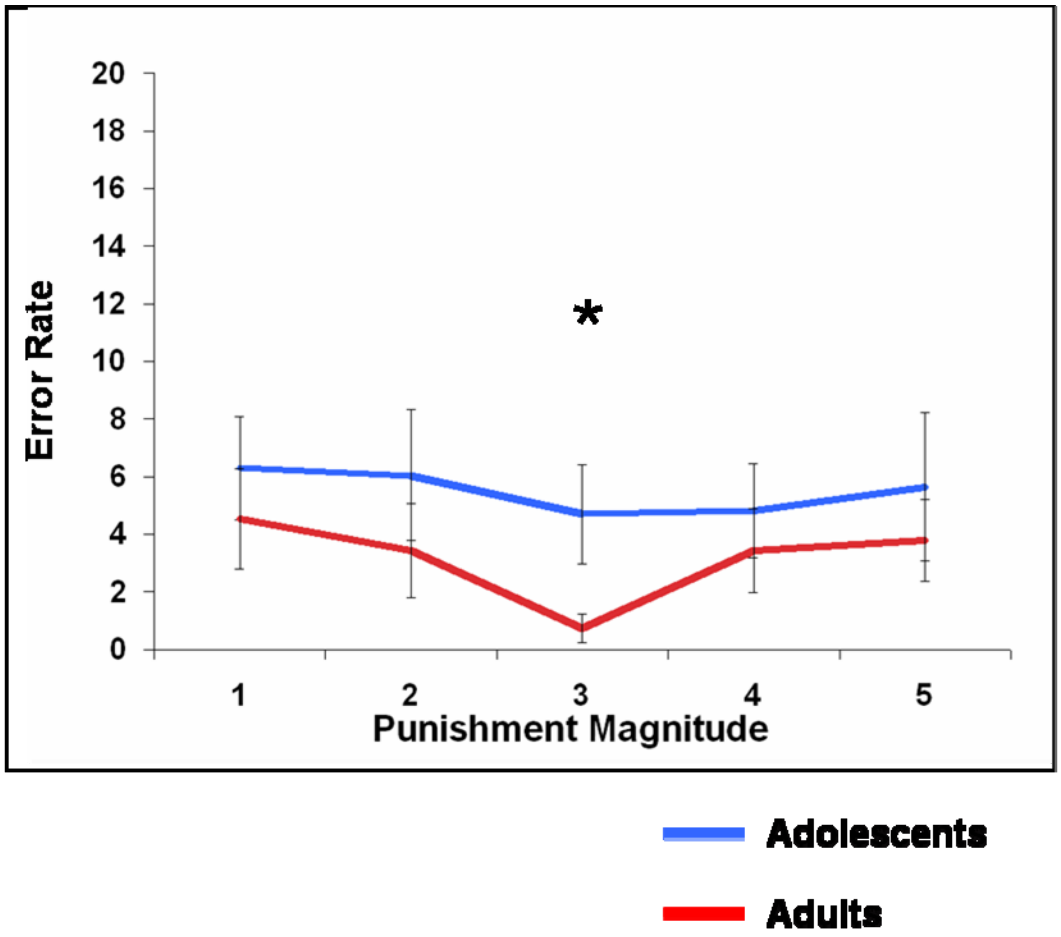

Figure 16. Error rates at each punishment magnitude.

Blue line = adolescents, red line = adults. Asterisk denotes significant ($p<0.05$) difference. Error bars represent +/- 1 standard error of the mean.

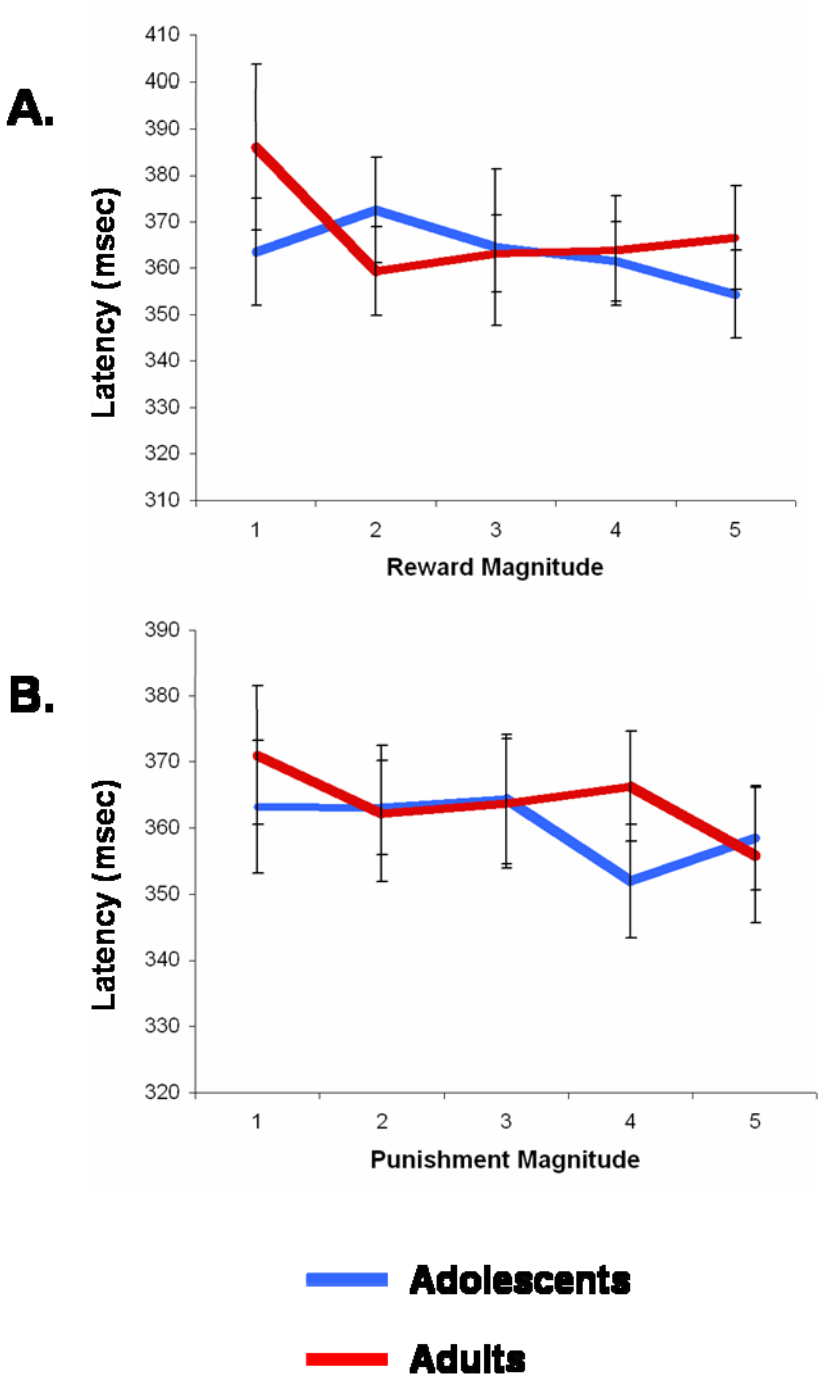

Figure 17. Latencies of correct antisaccades across (A) reward and (B) punishment magnitudes for adolescents (blue lines) and adults (red lines).

Error bars represent +/- 1 standard error of the mean.

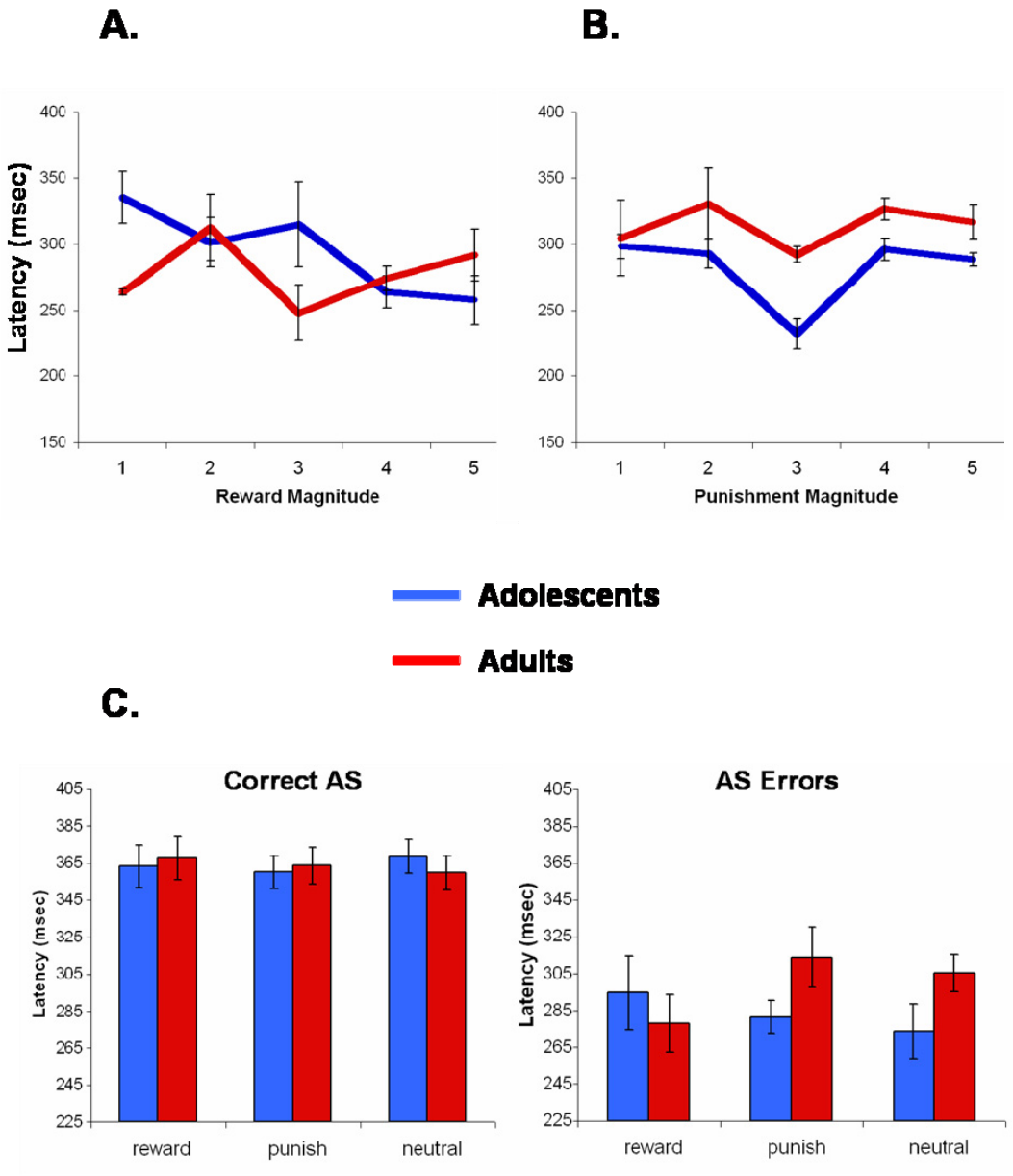

Figure 18. Latencies of prosaccade errors.

Latencies of errors across (A) reward and (B) punishment magnitudes. (C) Comparison of correct antisaccade (AS) latencies across incentive trial type (left bar graph) and antisaccade errors across trial type (right bar graph). Error bars represent +/- 1 standard error of the mean.

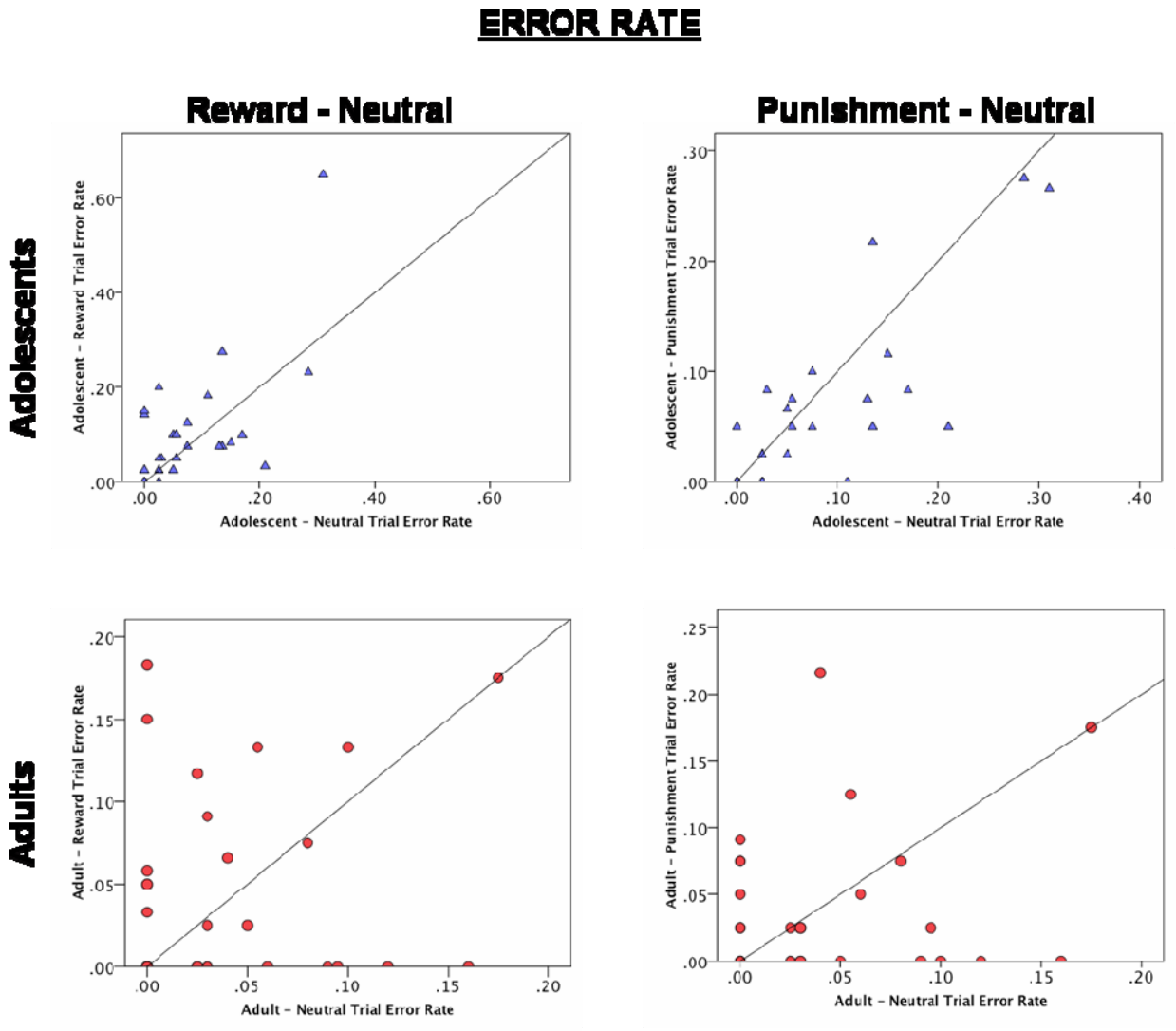

Figure 19. Comparison of individual subjects' error rates on valenced compared to neutral trials.

Data points below the diagonal line (defined by y = x) indicate higher values for neutral trials while points above the line indicated higher values for reward or punishment trials. Thus, subjects who performed better (made fewer errors) on trials with a reward or punishment contingency compared to neutral are indicated by points below the diagonal line.

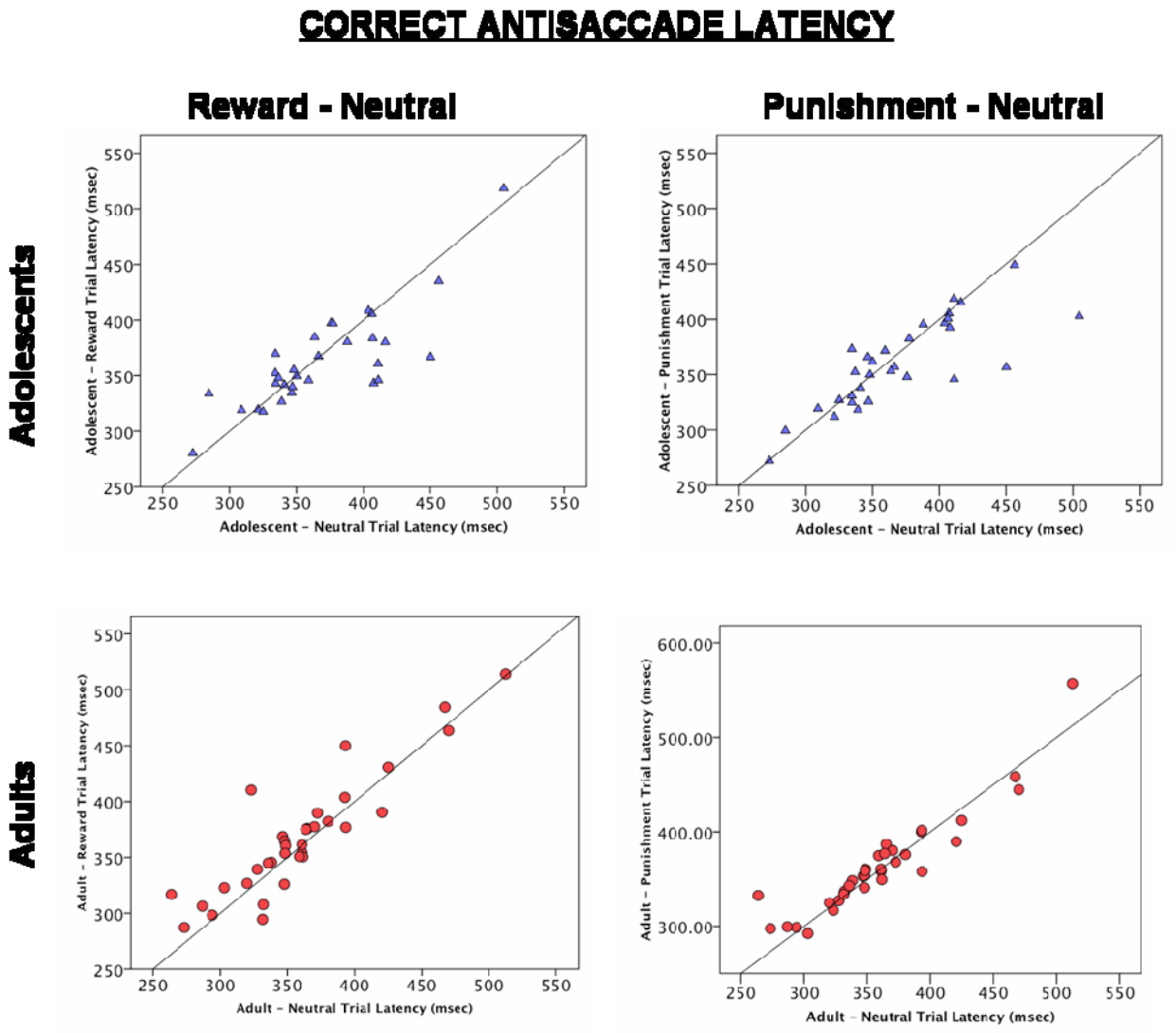

Figure 20. Comparison of individual subjects' correct antisaccade latencies on valenced compared to neutral trials.

Data points below the diagonal line (defined by y = x) indicate higher values for neutral trials while points above the line indicated higher values for reward or punishment trials. Thus, subjects who generated faster correct antisaccades (lower latencies) on trials with a reward or punishment contingency are indicated by points below the diagonal line.

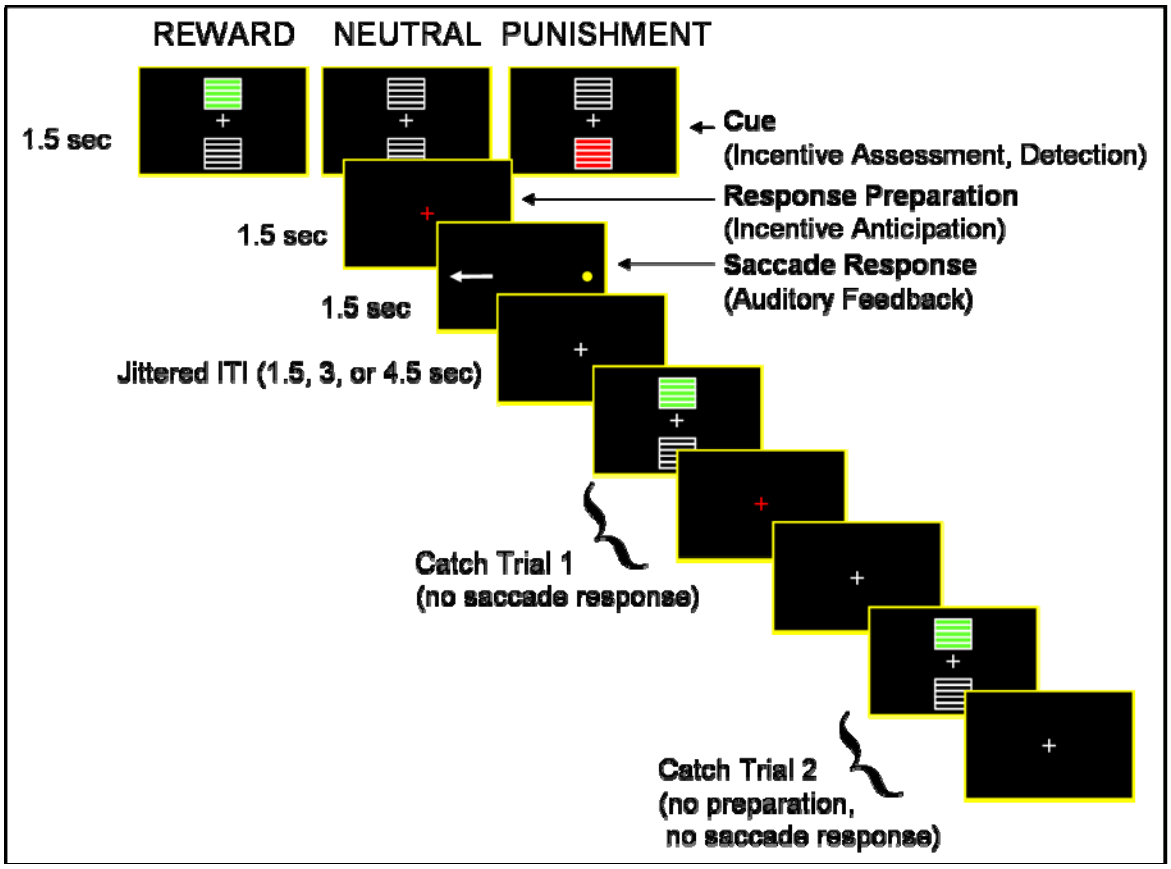

Figure 21. 'Bars' antisaccade (fMRI) task design.

Subjects first viewed an incentive-indicating cue for 1.5 sec, which consisted of either 5 green bars above the central fixation indicating a reward trial, 5 red bars below the central fixation indicating a punishment trial, or 5 gray bars indicating a neutral trial). Following the cue, the fixation cross turned red to indicate the response preparation period (1.5). Finally, a peripheral light appeared for the first 75msec of a 1.5sec saccade response period. Two variants of partial '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 sec) between all trials.

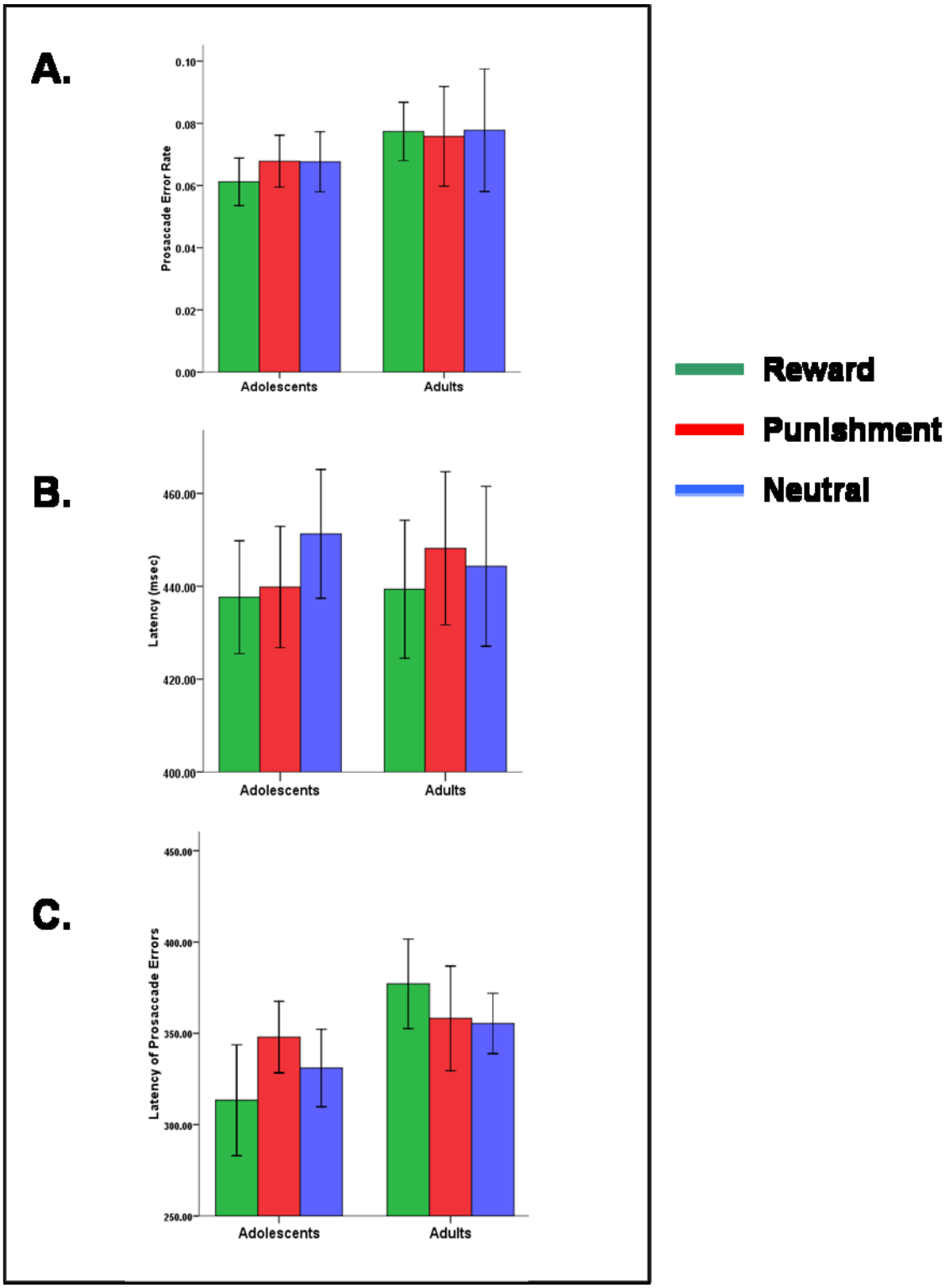

Figure 22. Results of eye data obtained during imaging.

A. Error rate, B. Correct antisaccade latency, C. Latencies of antisaccade errors. Error bars = +/-1 S.E.M.

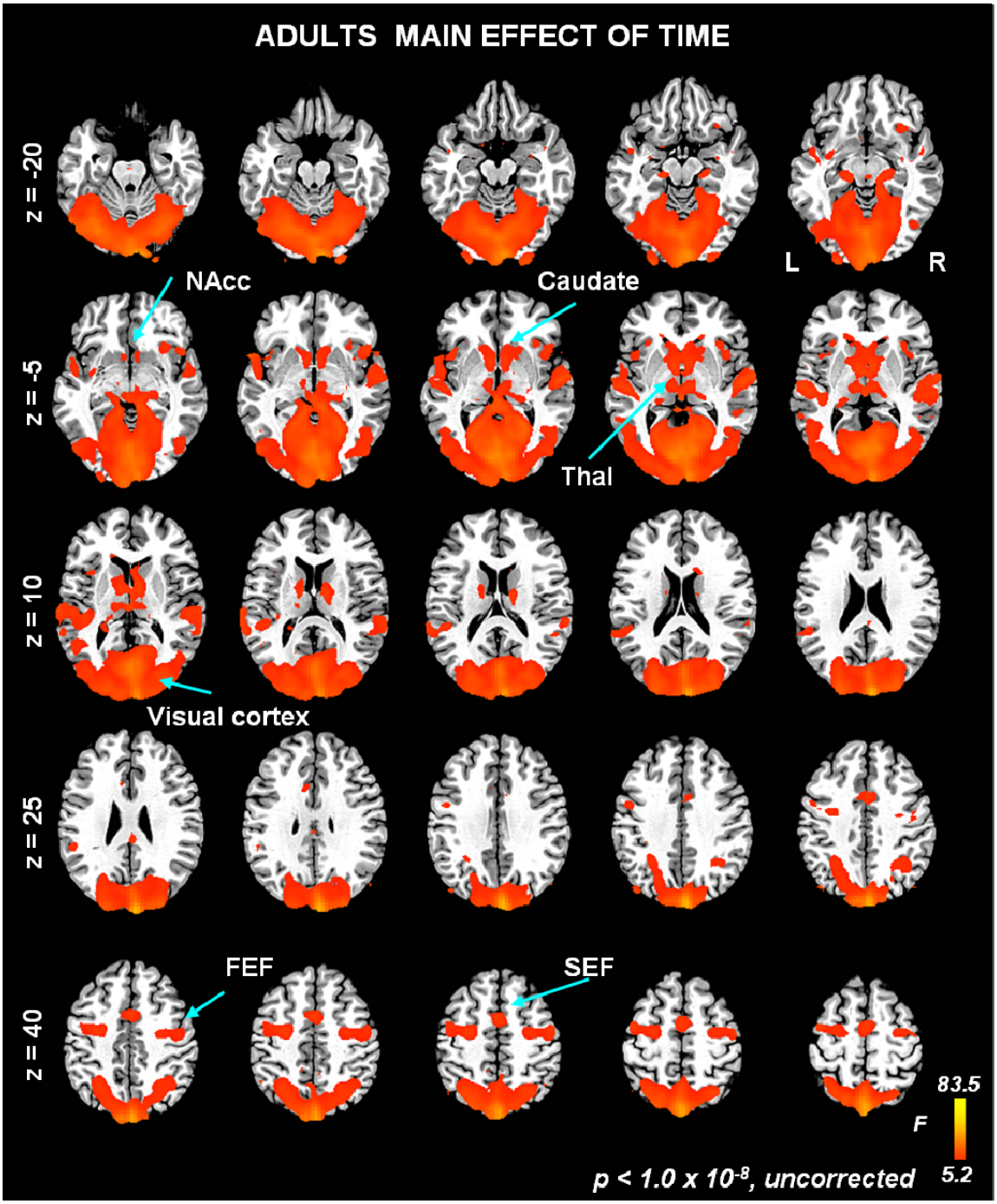

Figure 23. Adult 'main effect of time' maps, collapsed across incentive condition and trial epoch.

Abbreviations: NAcc = nucleus accumbens; Thal = thalamus; FEF = frontal eye field; SEF = supplementary eye field.

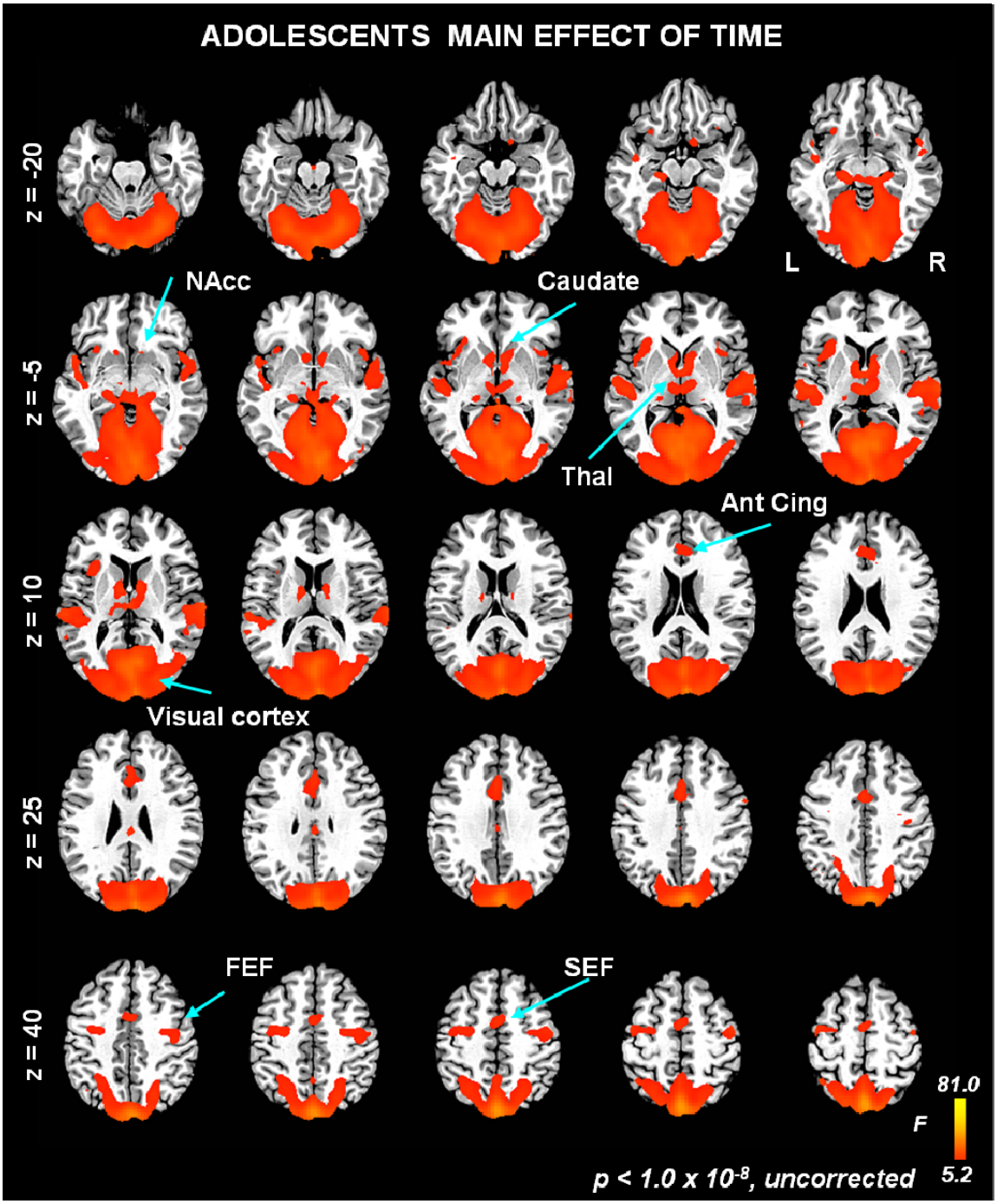

Figure 24. Adolescent 'main effect of time' maps, collapsed across incentive condition and trial epoch.

Abbreviations: NAcc = nucleus accumbens; Thal = thalamus; FEF = frontal eye field; SEF = supplementary eye field; Ant Cing = anterior cingulate.

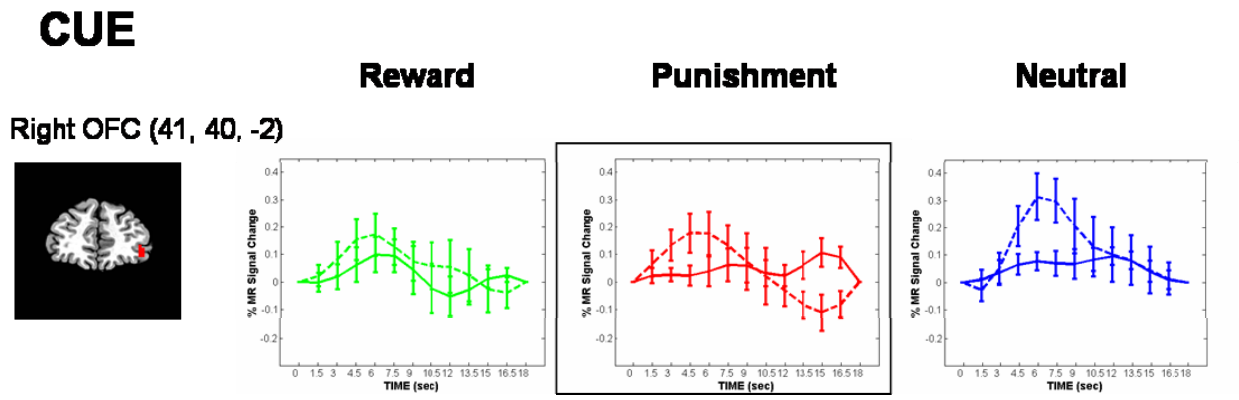

Figure 25. Incentive-related regions recruited during incentive cue that that show age- and/or incentive-related effects as determined from the omnibus ANOVA.

Time courses from reward trials are shown in green, punishment trials in red, and neutral trials in blue. Adult responses are represented by solid lines, adolescents by dashed lines. Boxes appear around time courses showing age-related effects for that incentive trial type. OFC = orbitofrontal cortex. Error bars = +/-1 S.E.M.

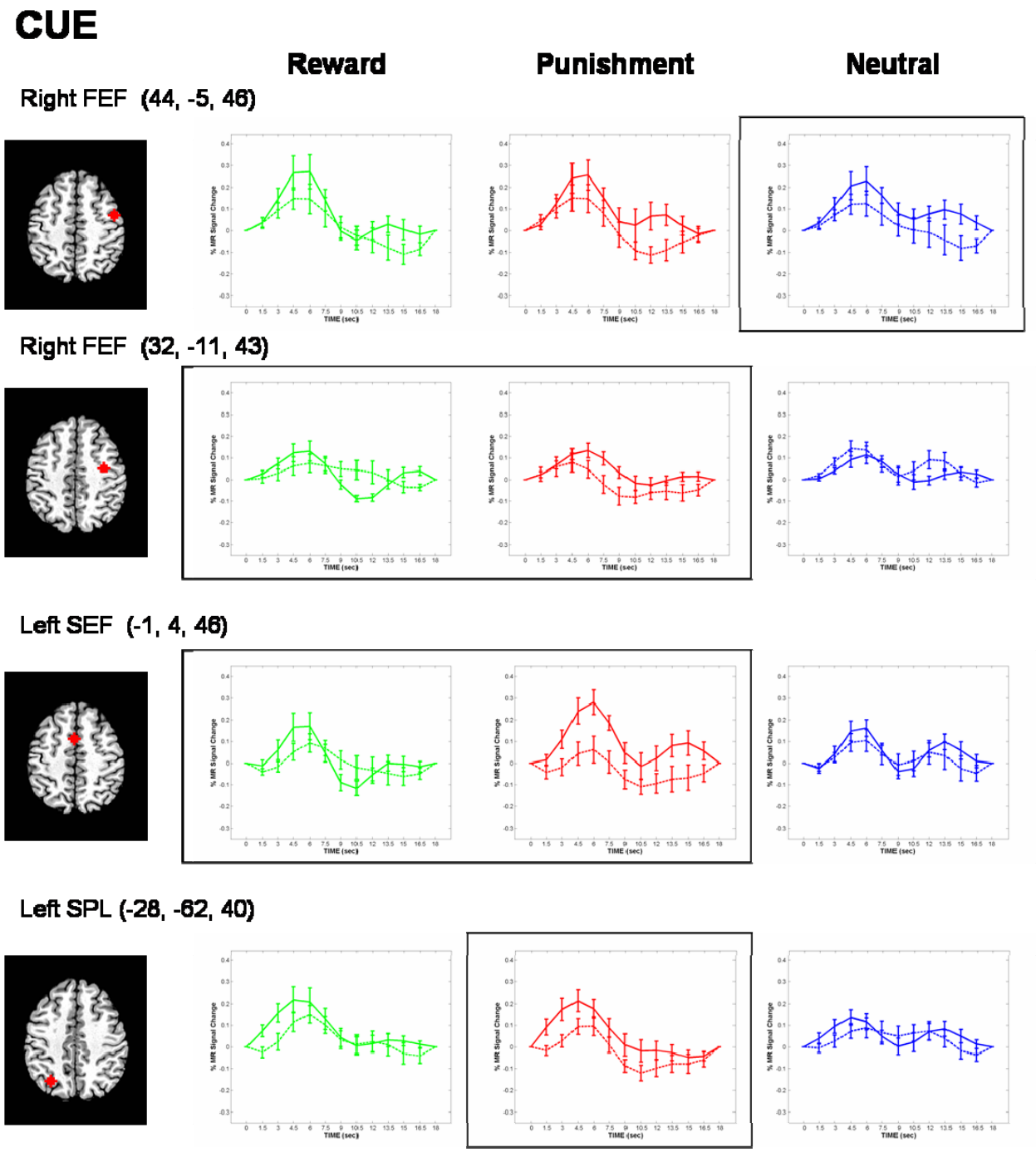

Figure 26. Oculomotor and/or inhibitory control regions recruited during incentive cue that show age- and/or incentive-related effects as determined from the omnibus ANOVA.

Abbreviations: FEF = frontal eye field; SEF = supplementary eye field; SPL = superior parietal lobule. Error bars = +/-1 S.E.M.

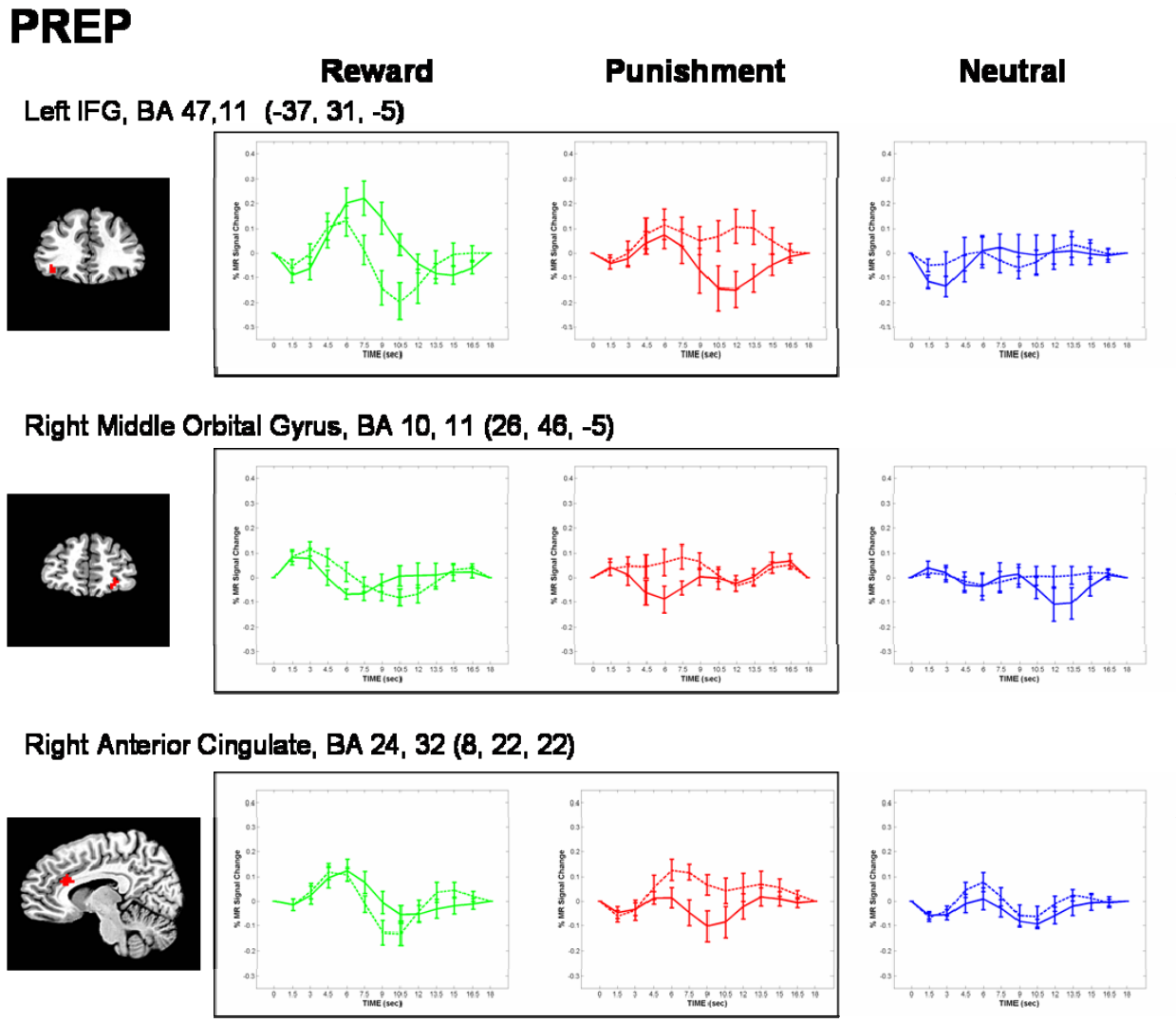

Figure 27. Incentive-related regions recruited during response preparation that show age- and/or incentive-related effects as determined from the omnibus ANOVA.

Time courses from reward trials are shown in green, punishment trials in red, and neutral trials in blue. Adult responses are represented by solid lines, adolescents by dashed lines. Boxes appear around time courses showing age-related effects for that incentive trial type. Abbreviations: IFG = inferior frontal gyrus. Error bars = +/-1 S.E.M.

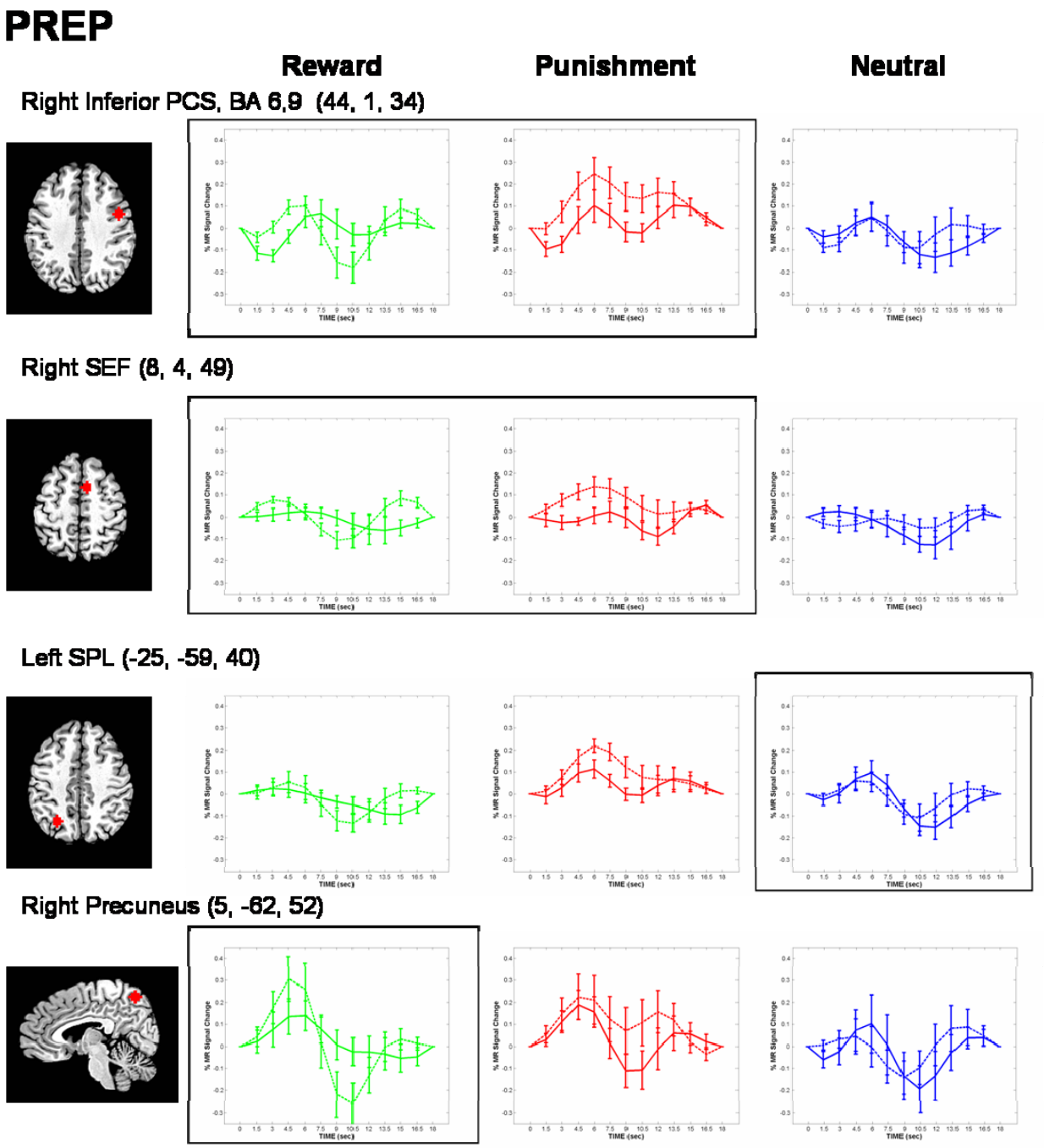

Figure 28. Oculomotor and/or inhibitory control regions recruited during response preparation that show age- and/or incentive-related effects as determined from the omnibus ANOVA.

Time courses from reward trials are shown in green, punishment trials in red, and neutral trials in blue. Adult responses are represented by solid lines, adolescents by dashed lines. Boxes appear around time courses showing age-related effects for that incentive trial type. Abbreviations: PCS = precentral sulcus; SEF = supplementary eye field; SPL = superior parietal lobule. Error bars = +/-1 S.E.M.

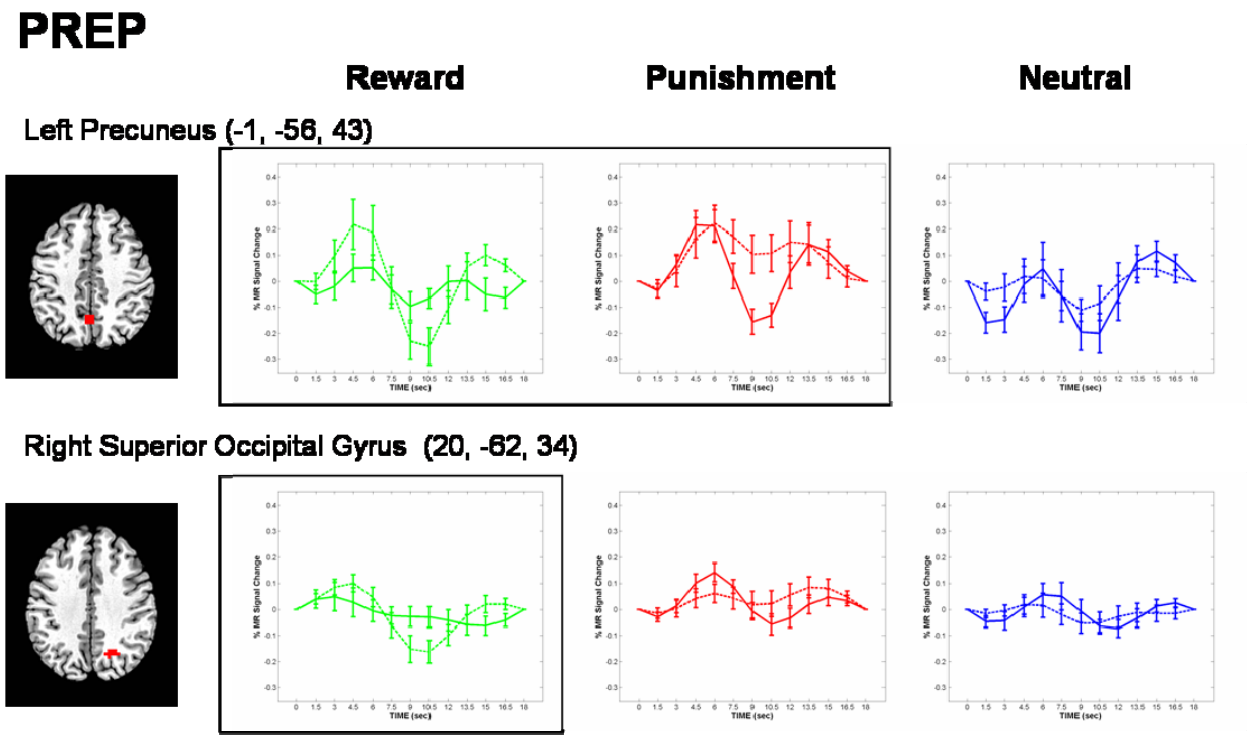

Figure 29. Additional oculomotor and/or inhibitory control regions recruited during response preparation that show age- and/or incentive-related effects as determined from the omnibus ANOVA.

Time courses from reward trials are shown in green, punishment trials in red, and neutral trials in blue. Adult responses are represented by solid lines, adolescents by dashed lines. Boxes appear around time courses showing age-related effects for that incentive trial type. Error bars = +/-1 S.E.M.

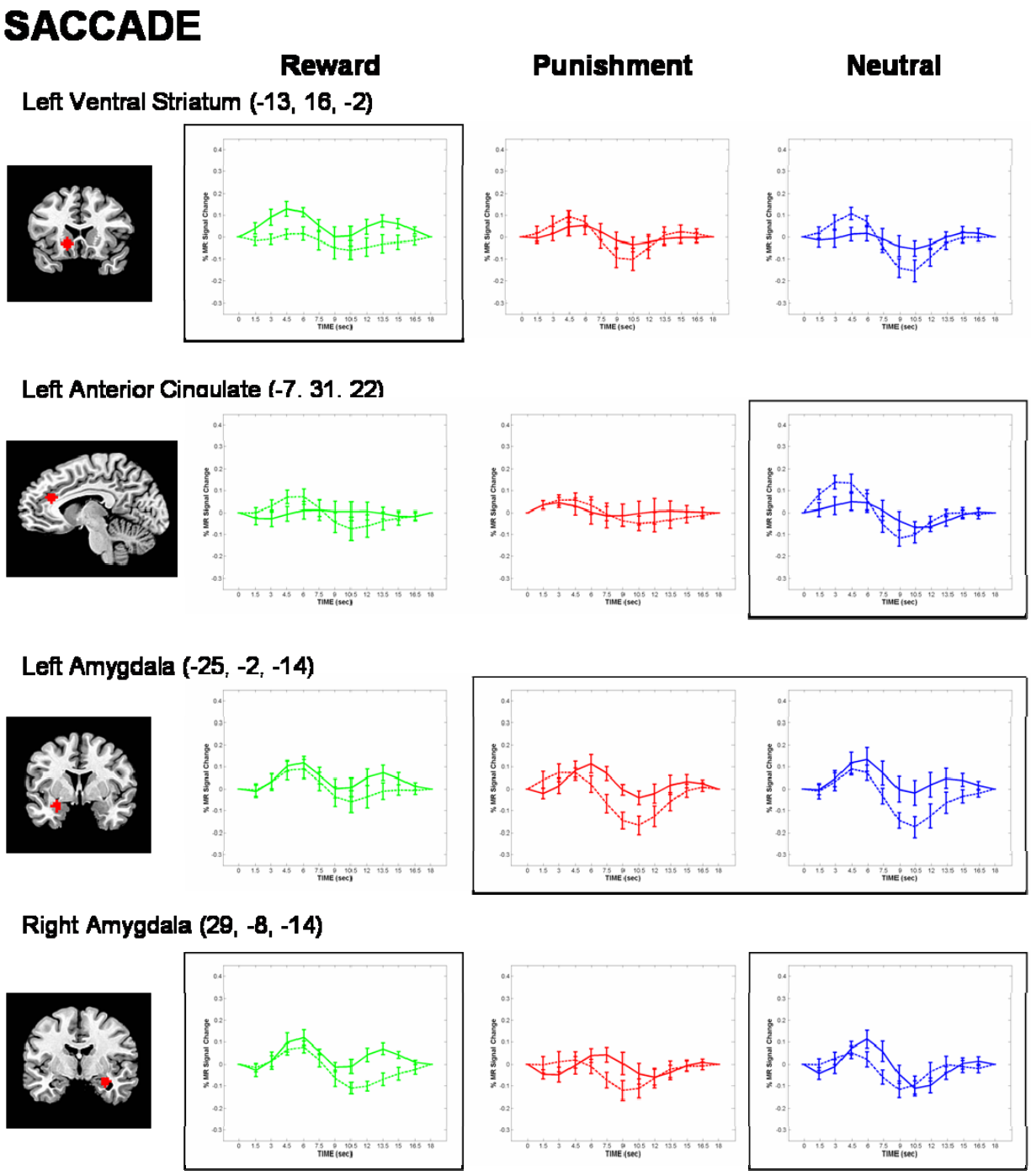

Figure 30. Incentive-related regions recruited during saccade response that show age- and/or incentive-related effects as determined from the omnibus ANOVA.

Time courses from reward trials are shown in green, punishment trials in red, and neutral trials in blue. Adult responses are represented by solid lines, adolescents by dashed lines. Boxes appear around time courses showing age-related effects for that incentive trial type. Error bars = +/-1 S.E.M.

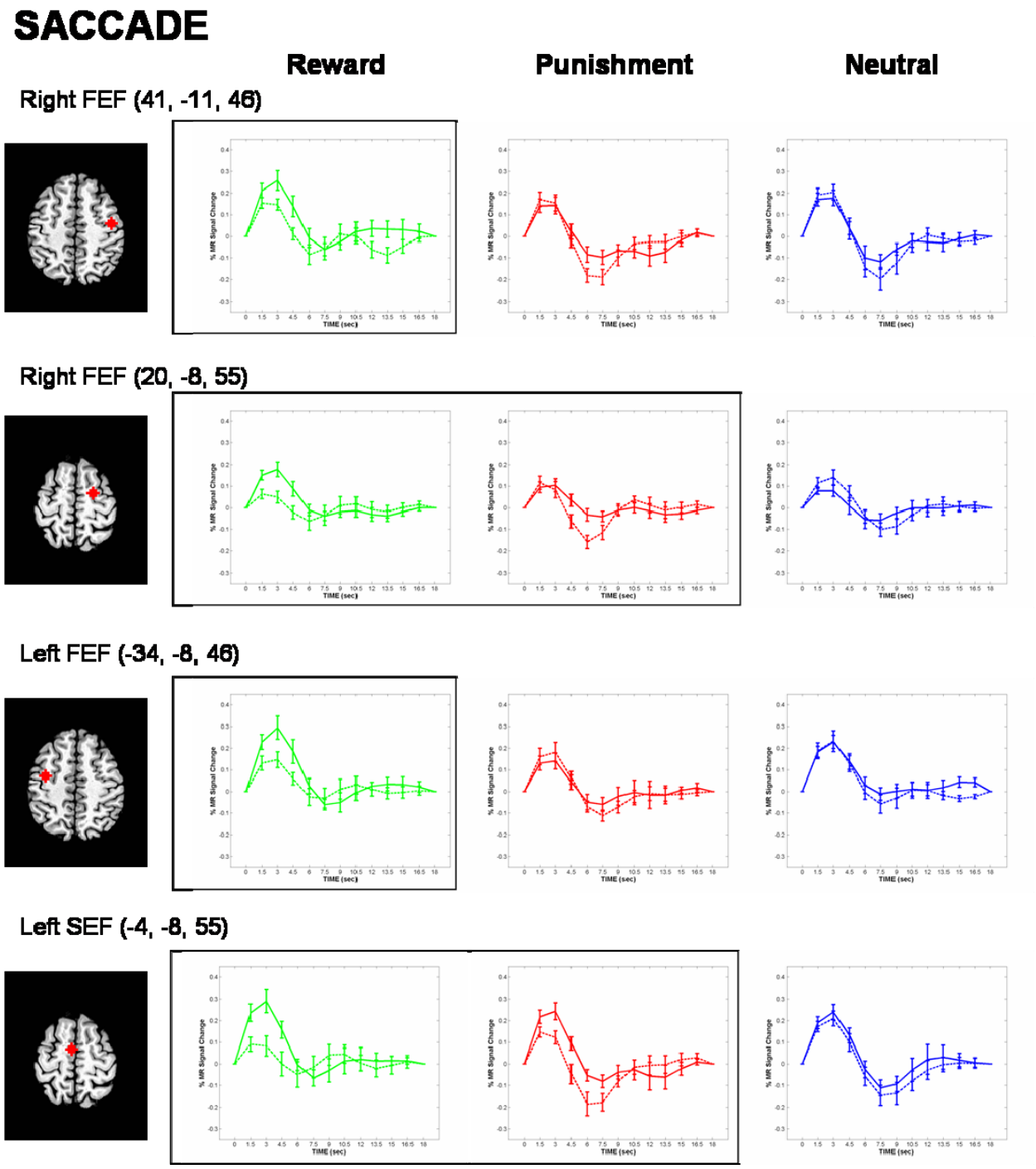

Figure 31. Oculomotor and/or inhibitory control regions recruited during saccade response that show age- and/or incentive-related effects as determined from the omnibus ANOVA.

Time courses from reward trials are shown in green, punishment trials in red, and neutral trials in blue. Adult responses are represented by solid lines, adolescents by dashed lines. Boxes appear around time courses showing age-related effects for that incentive trial type. Abbreviations: FEF = frontal eye field; SEF = supplementary eye field. Error bars = +/-1 S.E.M.

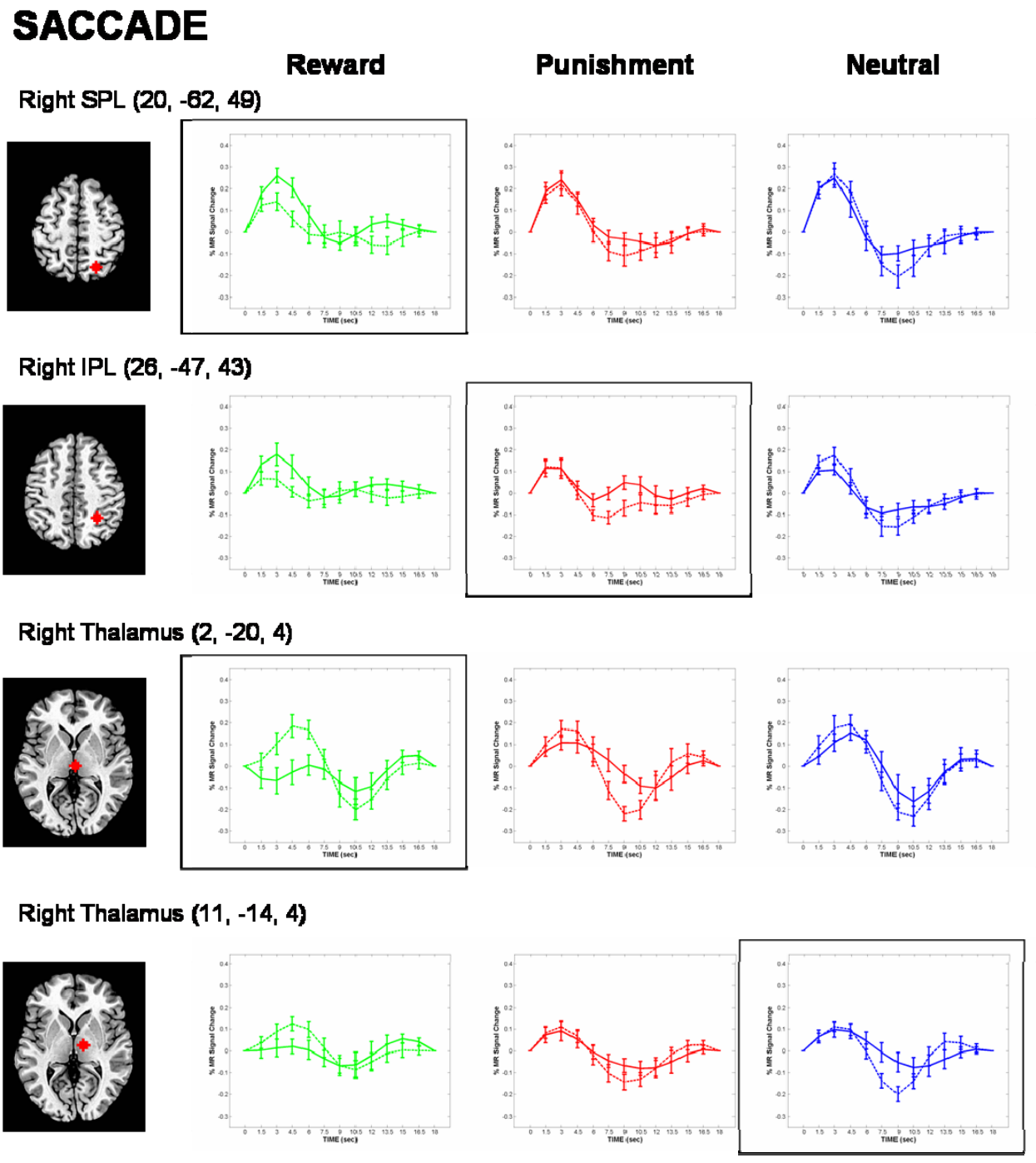

Figure 32. Additional oculomotor and/or inhibitory control regions recruited during saccade response that show age- and/or incentive-related effects as determined from the omnibus ANOVA.

Time courses from reward trials are shown in green, punishment trials in red, and neutral trials in blue. Adult responses are represented by solid lines, adolescents by dashed lines. Boxes appear around time courses showing age-related effects for that incentive trial type. Abbreviations: SPL = superior parietal lobule; IPL = inferior parietal lobule. Error bars = +/-1 S.E.M.

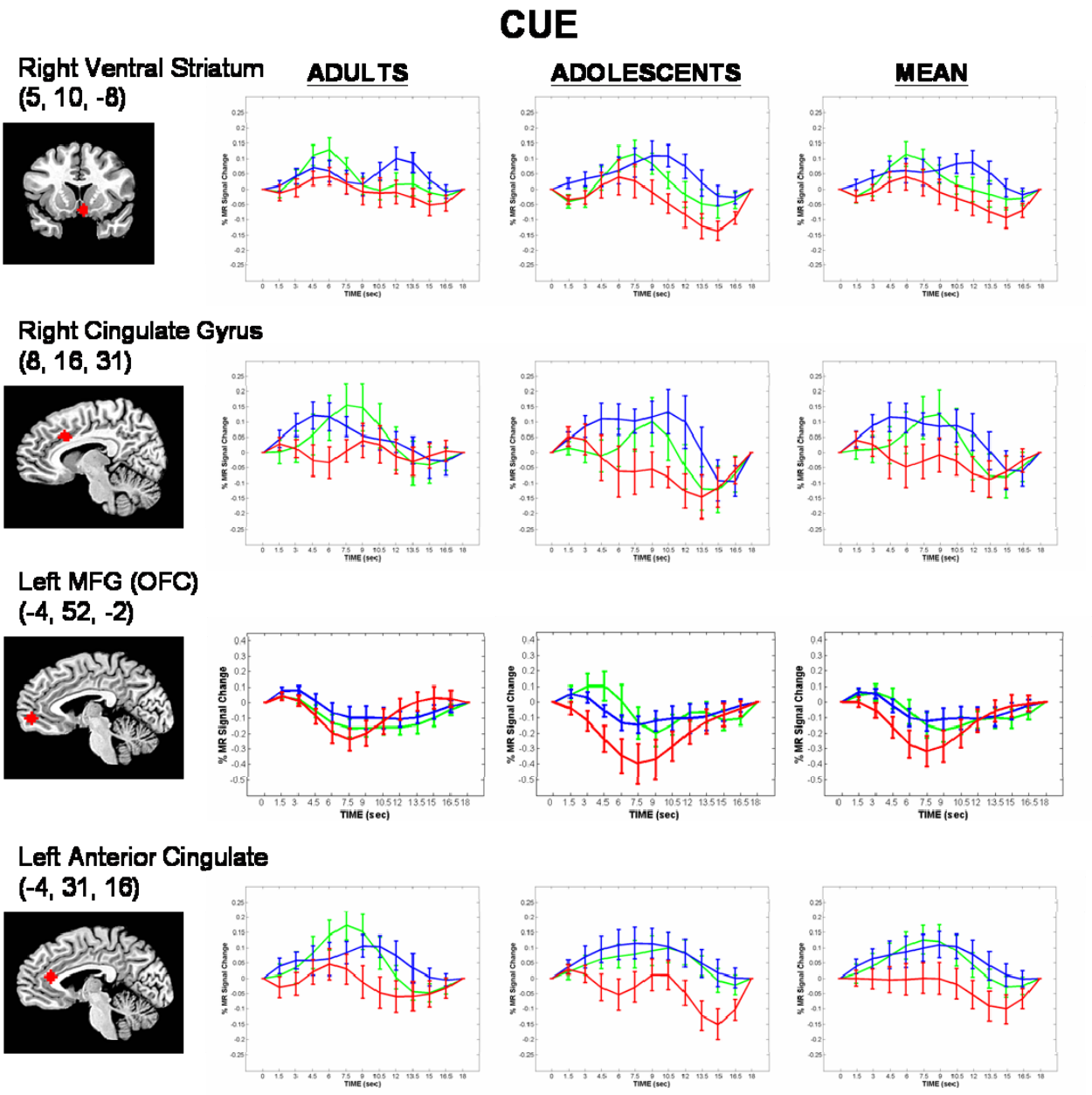

Figure 33. Cue Epoch: Reward-related brain ROI demonstrating significant main effects of valence and/or valence by time interactions.

The hemodynamic time courses are plotted for adults (left column) and adolescents (middle column) separately. Additionally, the adolescent and adult responses were averaged and plotted in the right column. For each plot, green lines = reward trial response, red lines = punishment trial response, and blue lines = neutral trial response. Abbreviations: MFG = medial frontal gyrus; OFC = orbitofrontal gyrus. Error bars = +/-1 S.E.M.

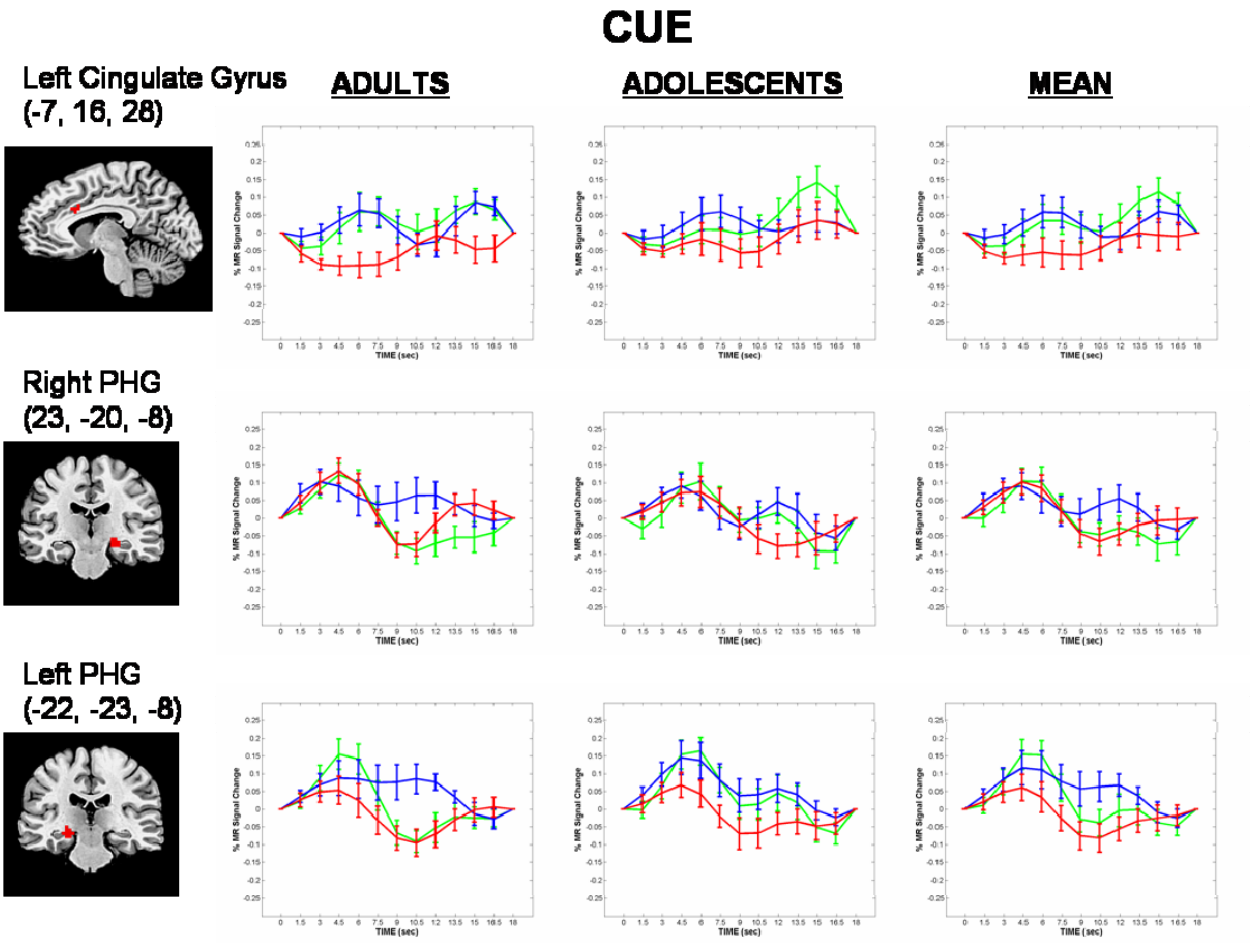

Figure 34. Cue Epoch: Additional reward-related brain ROI demonstrating significant main effects of valence and/or valence by time interactions.

The hemodynamic time courses are plotted for adults (left column) and adolescents (middle column) separately. Additionally, the adolescent and adult responses were averaged and plotted in the right column. For each plot, green lines = reward trial response, red lines = punishment trial response, and blue lines = neutral trial response. Abbreviations: PHG = parahippocampal gyrus. Error bars = +/-1 S.E.M.

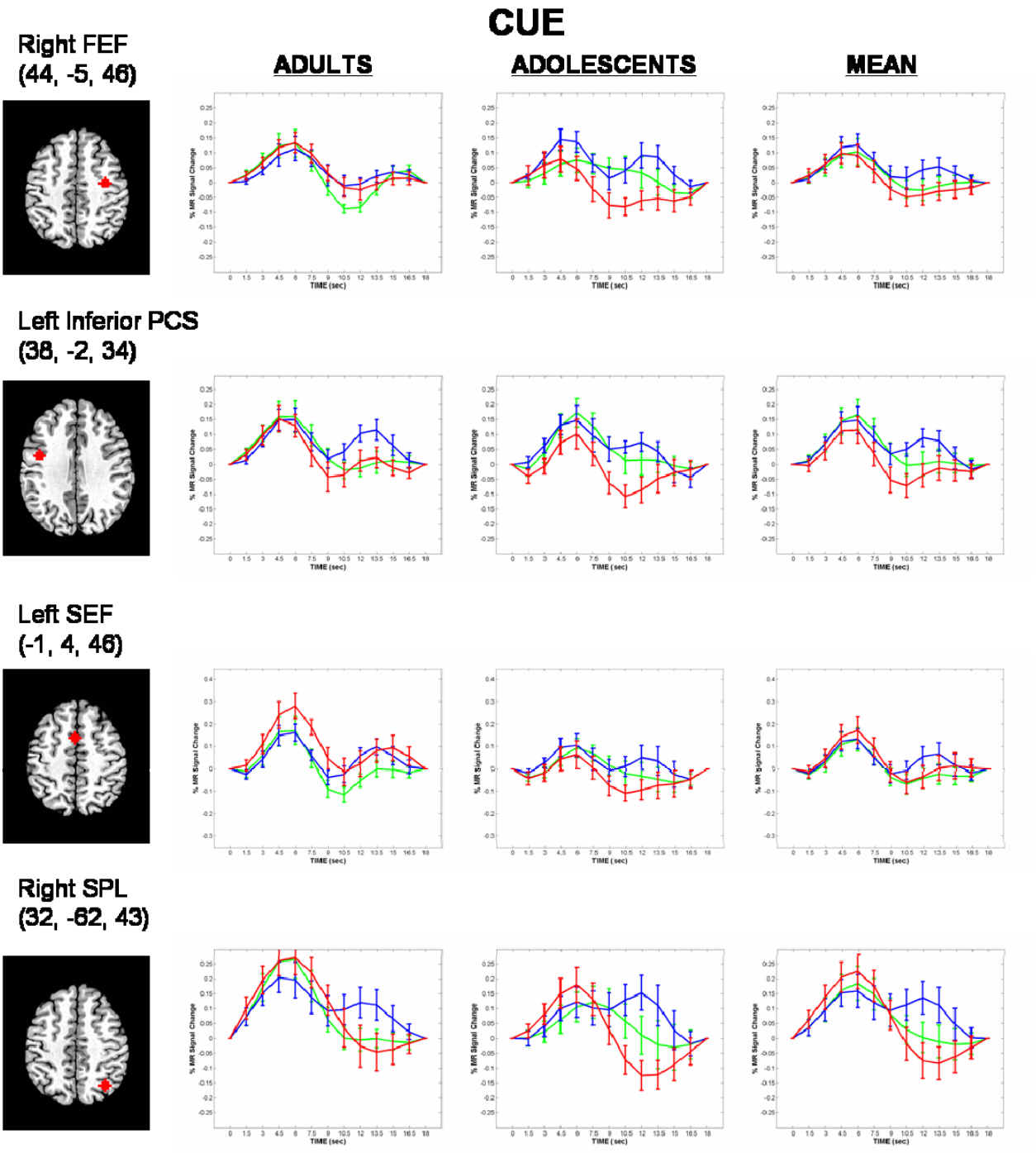

Figure 35. Cue Epoch: Oculomotor control-related brain ROI demonstrating significant main effects of valence and/or valence by time interactions.

The hemodynamic time courses are plotted for adults (left column) and adolescents (middle column) separately. Additionally, the adolescent and adult responses were averaged and plotted in the right column. For each plot, green lines = reward trial response, red lines = punishment trial response, and blue lines = neutral trial response. Abbreviations: FEF = frontal eye field; PCS = precentral sulcus; SEF = supplementary eye field; SPL = superior parietal lobule. Error bars = +/-1 S.E.M.

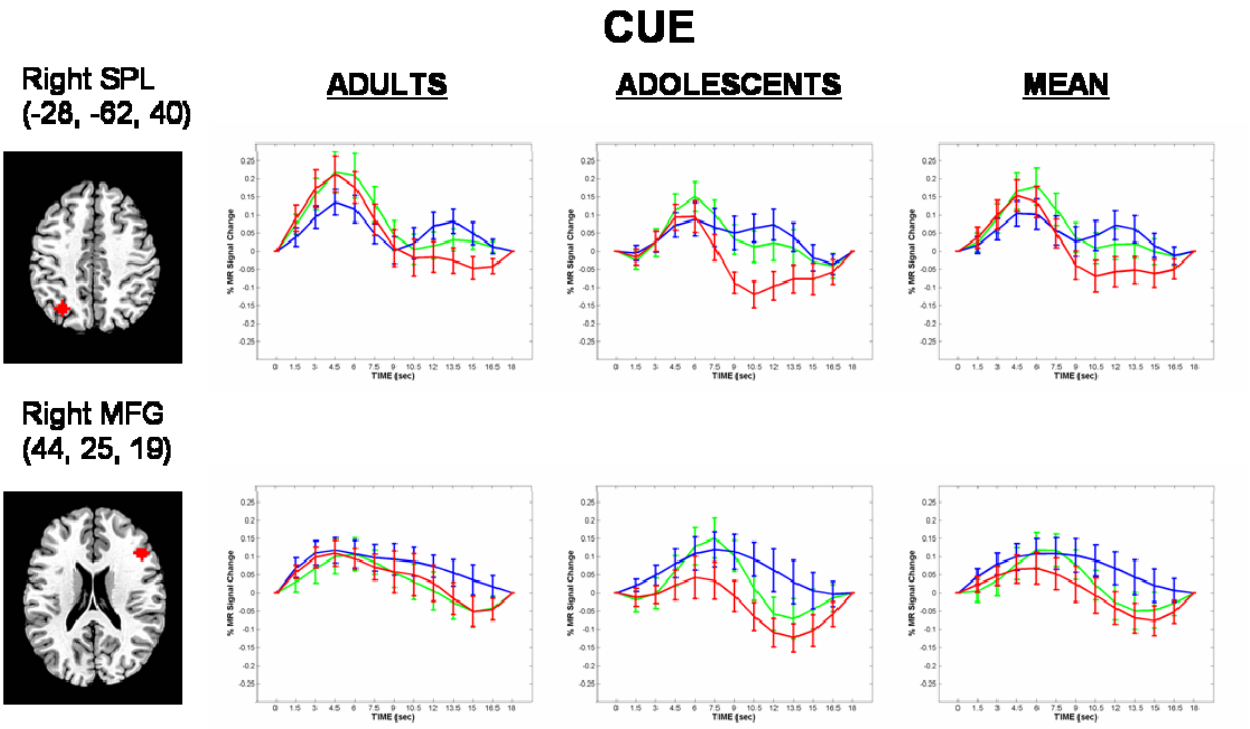

Figure 36. Cue Epoch: Additional oculomotor control-related brain ROI demonstrating significant main effects of valence and/or valence by time interactions.

The hemodynamic time courses are plotted for adults (left column) and adolescents (middle column) separately. Additionally, the adolescent and adult responses were averaged and plotted in the right column. For each plot, green lines = reward trial response, red lines = punishment trial response, and blue lines = neutral trial response. Abbreviations: SPL = superior parietal lobule; MFG = middle frontal gyrus. Error bars = +/-1 S.E.M.

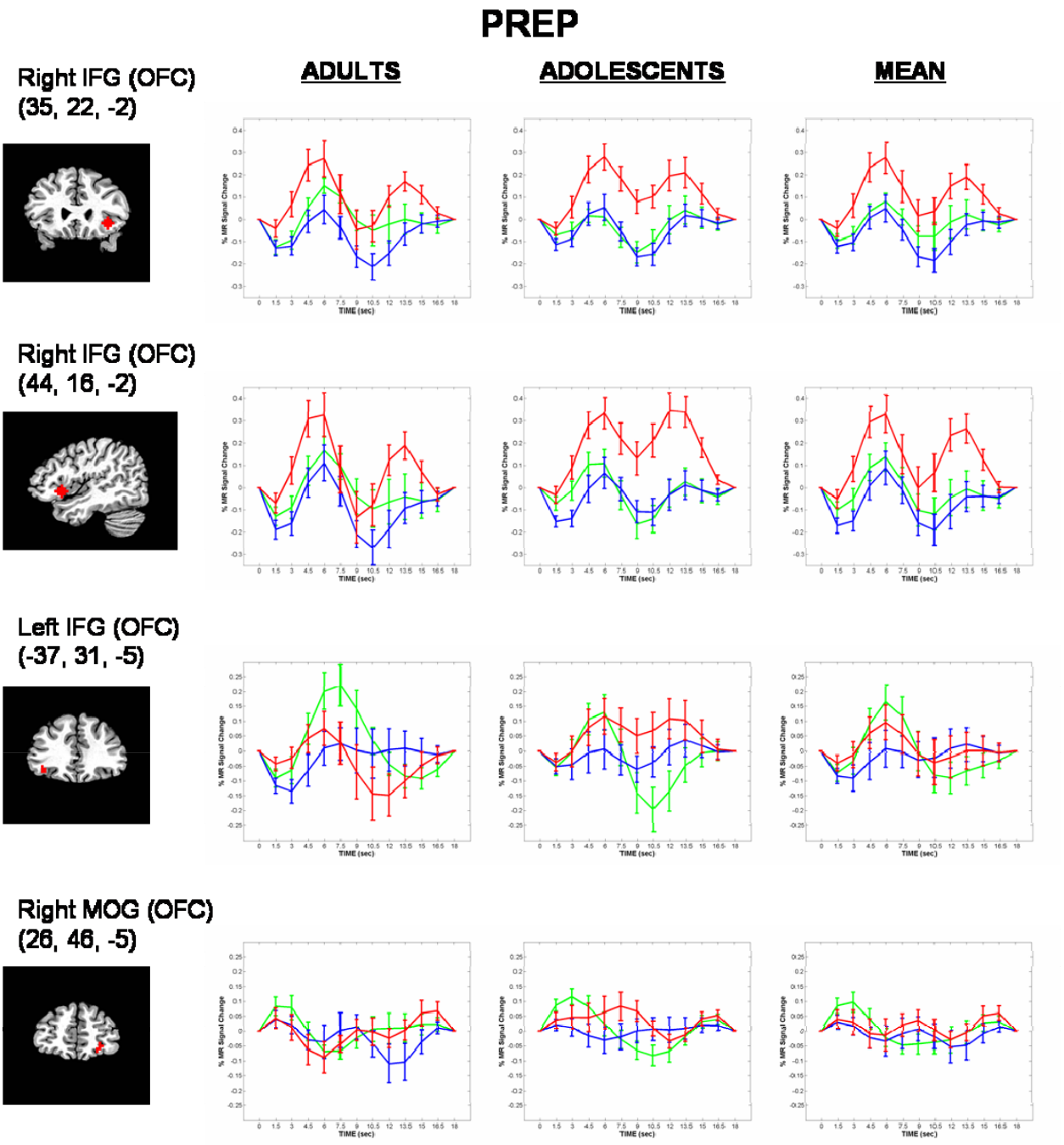

Figure 37. Preparatory Epoch: Reward-related brain ROI demonstrating significant main effects of valence and/or valence by time interactions.

The hemodynamic time courses are plotted for adults (left column) and adolescents (middle column) separately. Additionally, the adolescent and adult responses were averaged and plotted in the right column. For each plot, green lines = reward trial response, red lines = punishment trial response, and blue lines = neutral trial response. Abbreviations: IFG = inferior frontal gyrus; OFC = orbitofrontal cortex; MOG = middle occipital gyrus. Error bars = +/-1 S.E.M.

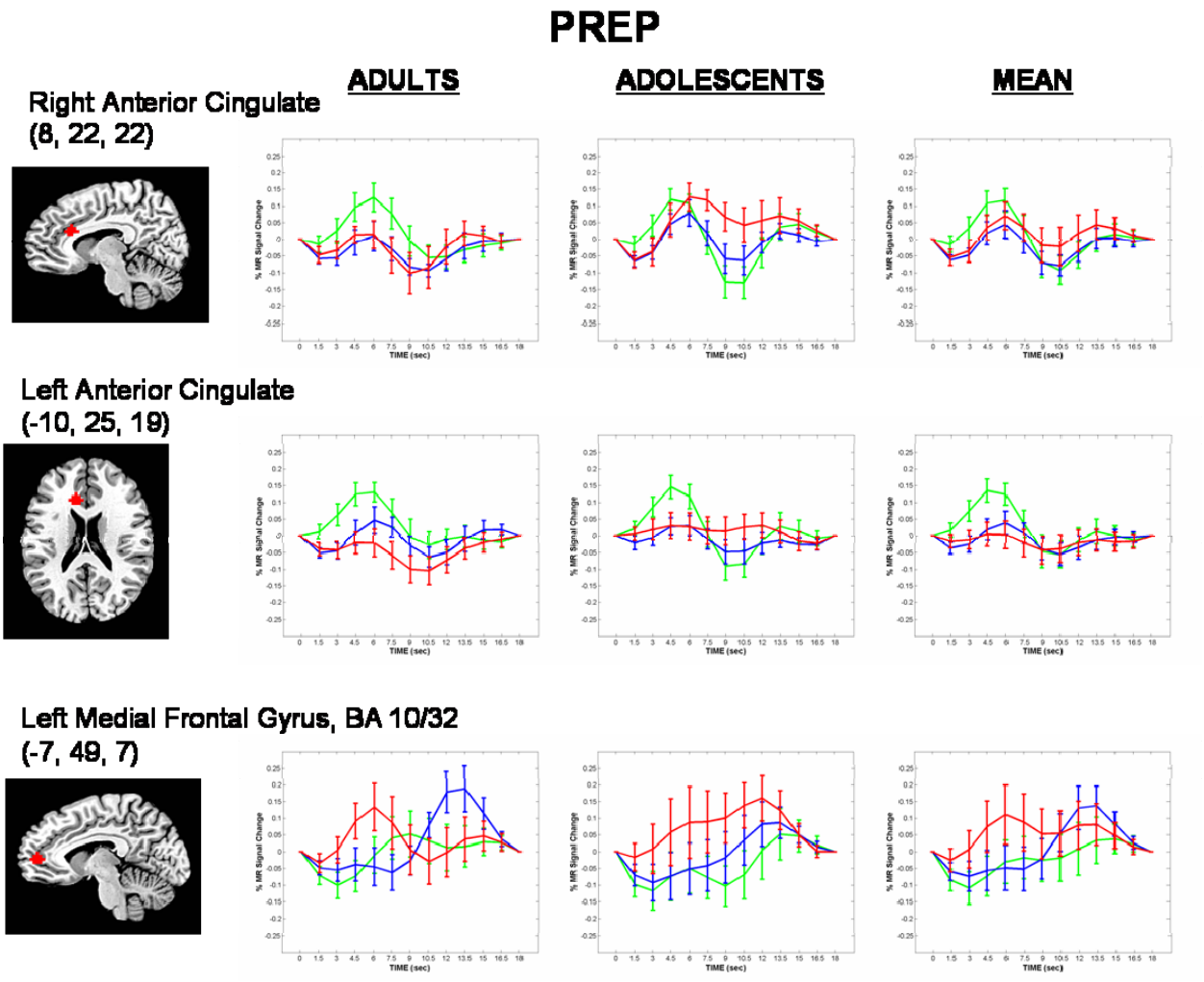

Figure 38. Preparatory Epoch: Additional reward-related brain ROI demonstrating significant main effects of valence and/or valence by time interactions.

The hemodynamic time courses are plotted for adults (left column) and adolescents (middle column) separately. Additionally, the adolescent and adult responses were averaged and plotted in the right column. For each plot, green lines = reward trial response, red lines = punishment trial response, and blue lines = neutral trial response. Error bars = +/-1 S.E.M.

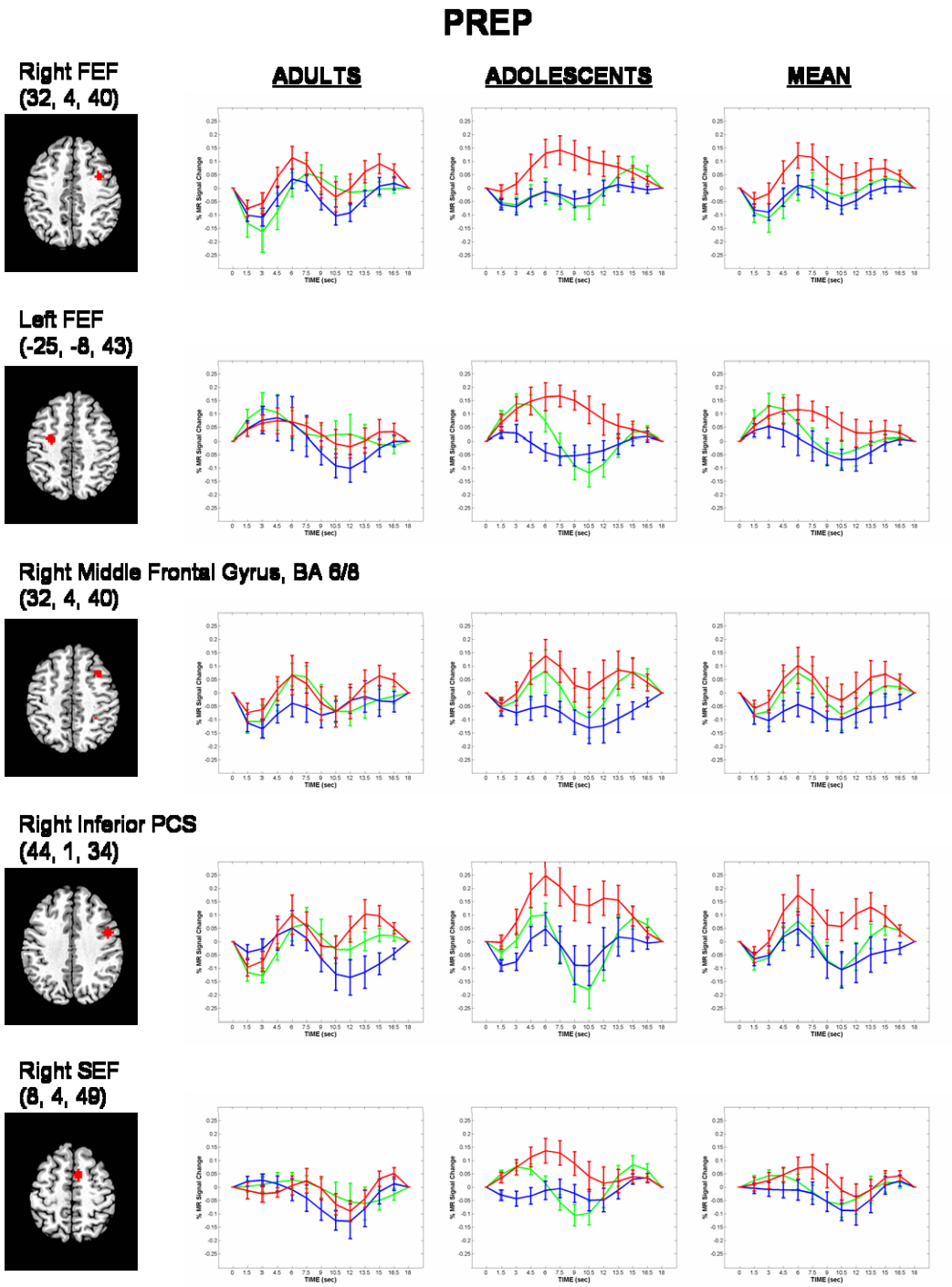

Figure 39. Preparatory Epoch: Oculomotor control-related brain ROI demonstrating significant main effects of valence and/or valence by time interactions.

The hemodynamic time courses are plotted for adults (left column) and adolescents (middle column) separately. Additionally, the adolescent and adult responses were averaged and plotted in the right column. For each plot, green lines = reward trial response, red lines = punishment trial response, and blue lines = neutral trial response. Abbreviations: FEF = frontal eye field; PCS = precentral sulcus; SEF = supplementary eye field. Error bars = +/-1 S.E.M.

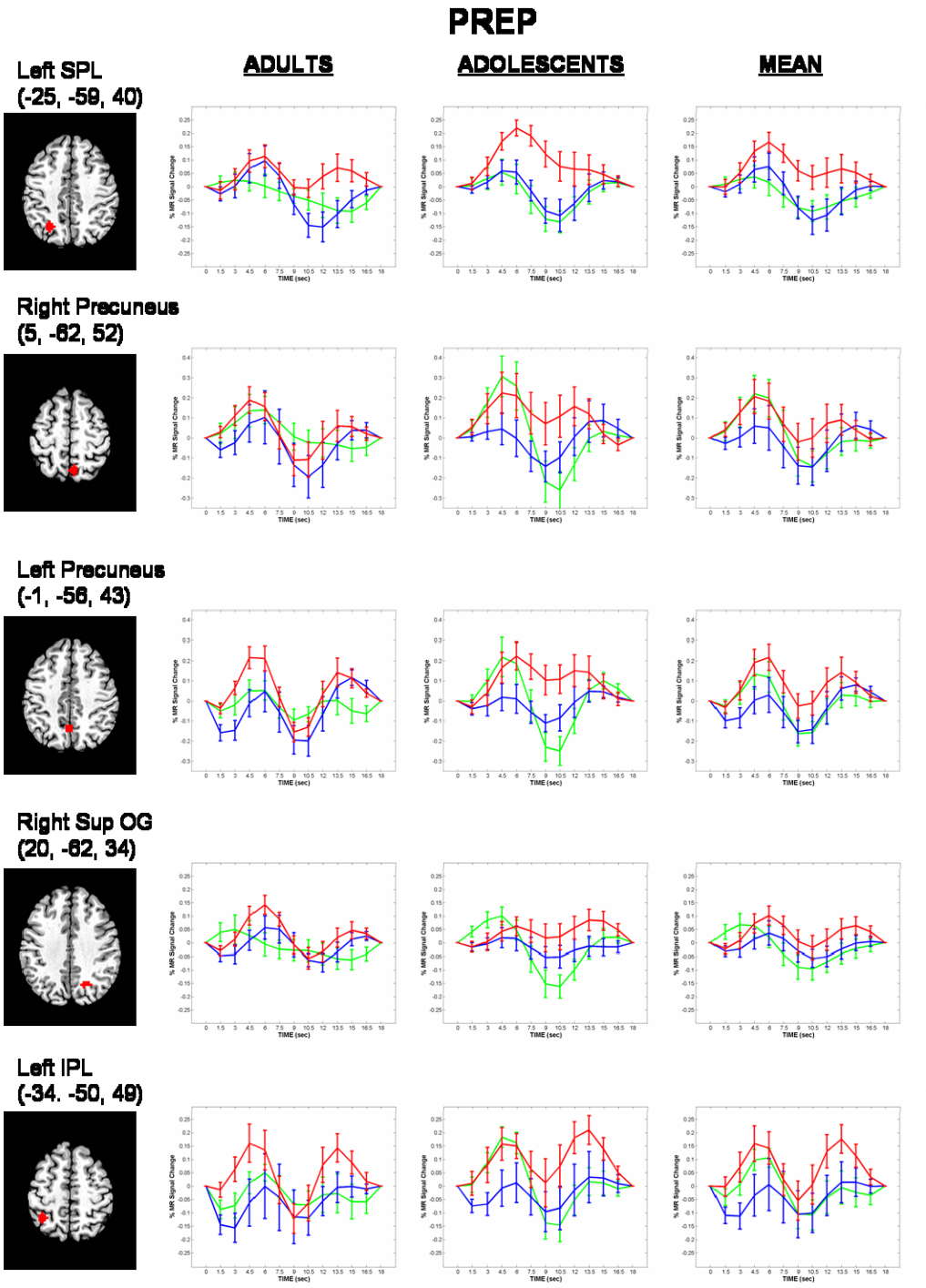

Figure 40. Preparatory Epoch: Additional oculomotor control-related brain ROI demonstrating significant main effects of valence and/or valence by time interactions.

The hemodynamic time courses are plotted for adults (left column) and adolescents (middle column) separately. Additionally, the adolescent and adult responses were averaged and plotted in the right column. For each plot, green lines = reward trial response, red lines = punishment trial response, and blue lines = neutral trial response. Abbreviations: SPL = superior parietal lobule; Sup OG: superior occipital gyrus; IPL = inferior parietal lobule. Error bars = +/-1 S.E.M.

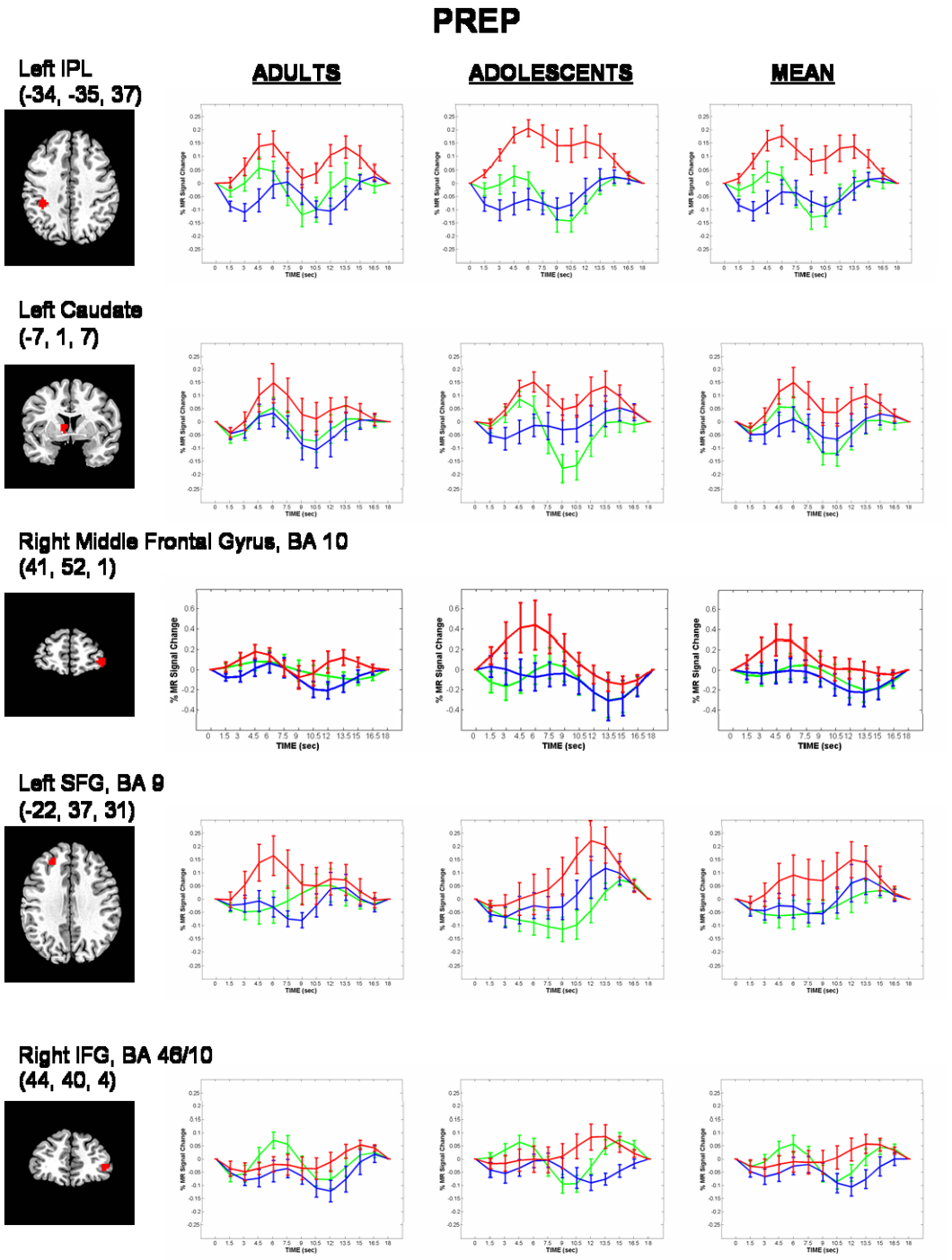

Figure 41. Additional oculomotor control-related brain ROI demonstrating significant main effects of valence and/or valence by time interactions.

The hemodynamic time courses are plotted for adults (left column) and adolescents (middle column) separately. Additionally, the adolescent and adult responses were averaged and plotted in the right column. For each plot, green lines = reward trial response, red lines = punishment trial response, and blue lines = neutral trial response. Abbreviations: IPL = inferior parietal lobule; SFG = superior frontal gyrus; IFG = inferior frontal gyrus. Error bars = +/-1 S.E.M.

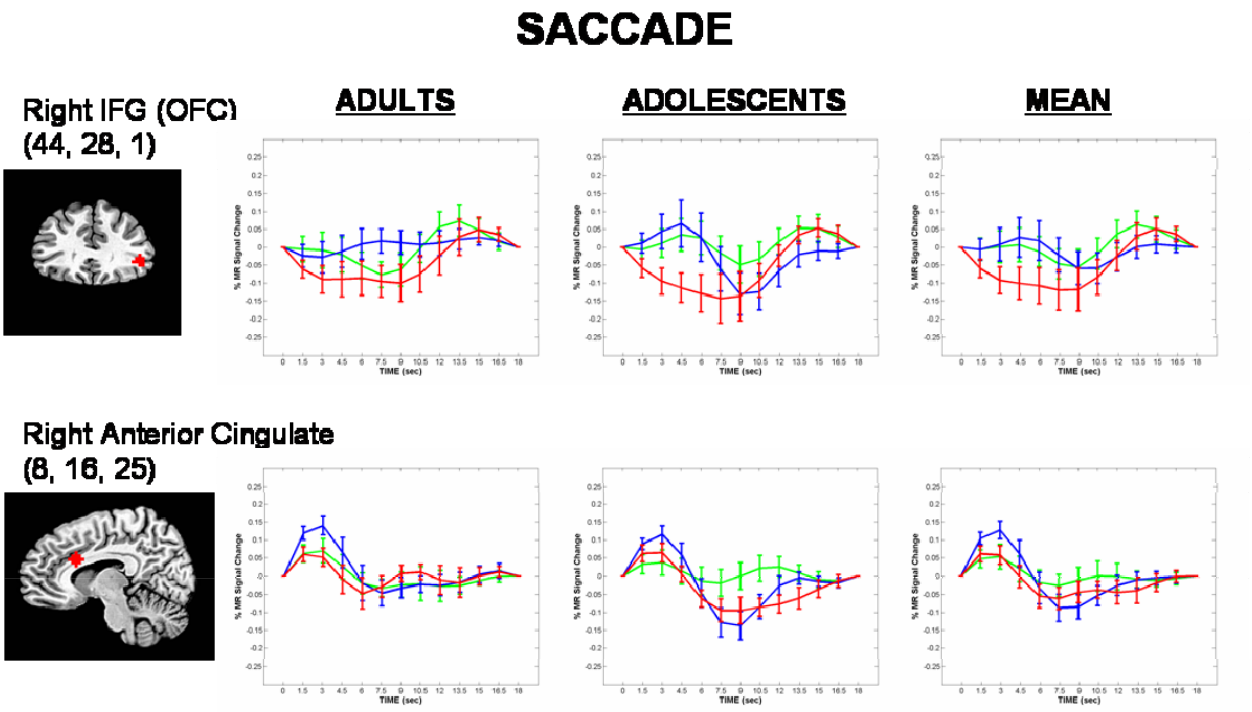

Figure 42. Saccade Response Epoch: Reward-related brain ROI demonstrating significant main effects of valence and/or valence by time interactions.

The hemodynamic time courses are plotted for adults (left column) and adolescents (middle column) separately. Additionally, the adolescent and adult responses were averaged and plotted in the right column. For each plot, green lines = reward trial response, red lines = punishment trial response, and blue lines = neutral trial response. Abbreviations: IFG = inferior frontal gyrus; OFC = orbitofrontal cortex. Error bars = +/-1 S.E.M.

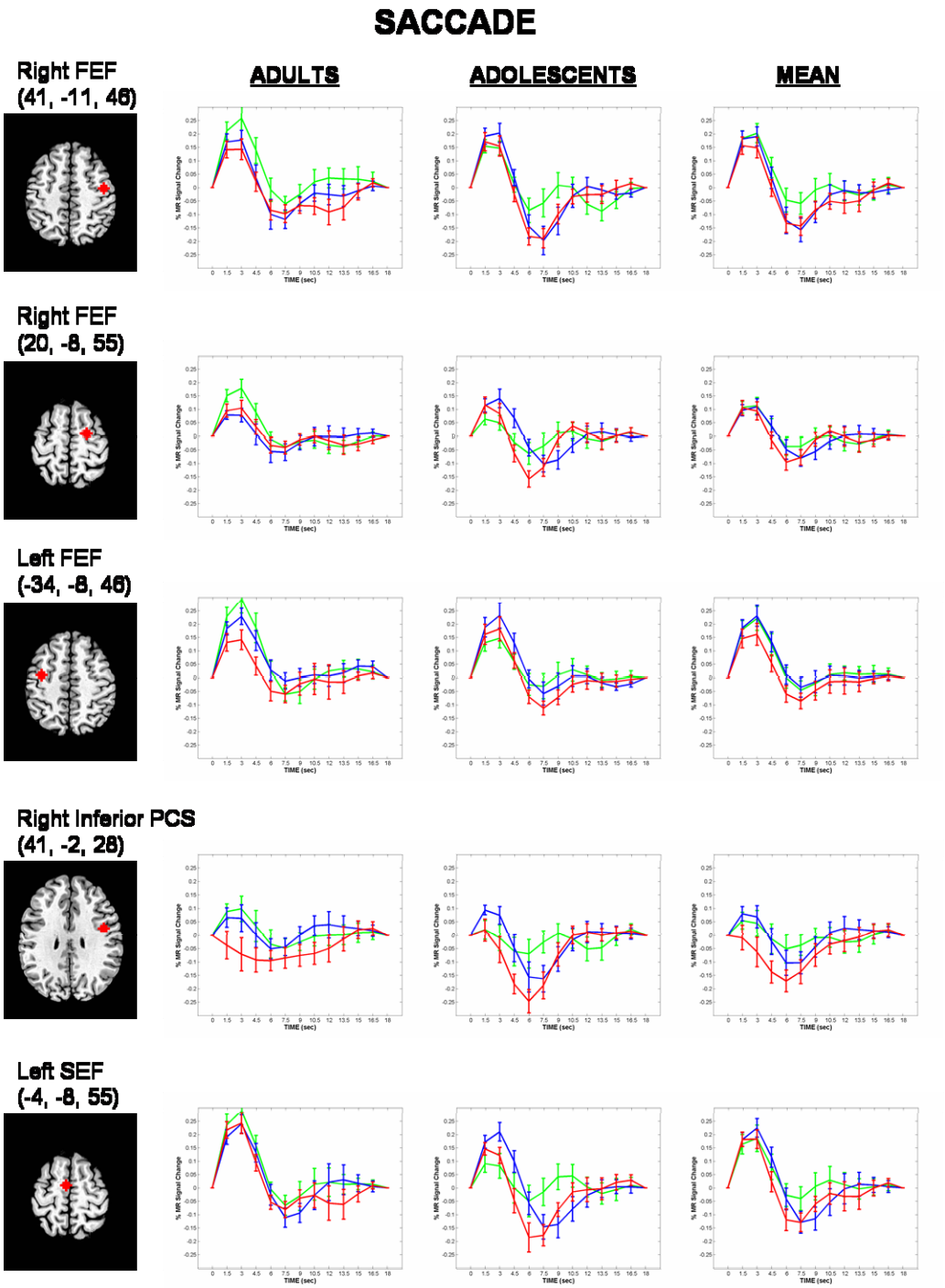

Figure 43. Saccade Response Epoch: Oculomotor control-related brain ROI demonstrating significant main effects of valence and/or valence by time interactions.

The hemodynamic time courses are plotted for adults (left column) and adolescents (middle column) separately. Additionally, the adolescent and adult responses were averaged and plotted in the right column. For each plot, green lines = reward trial response, red lines = punishment trial response, and blue lines = neutral trial response. Abbreviations: FEF = frontal eye field; PCS = precentral sulcus; SEF = supplementary eye field. Error bars = +/-1 S.E.M.

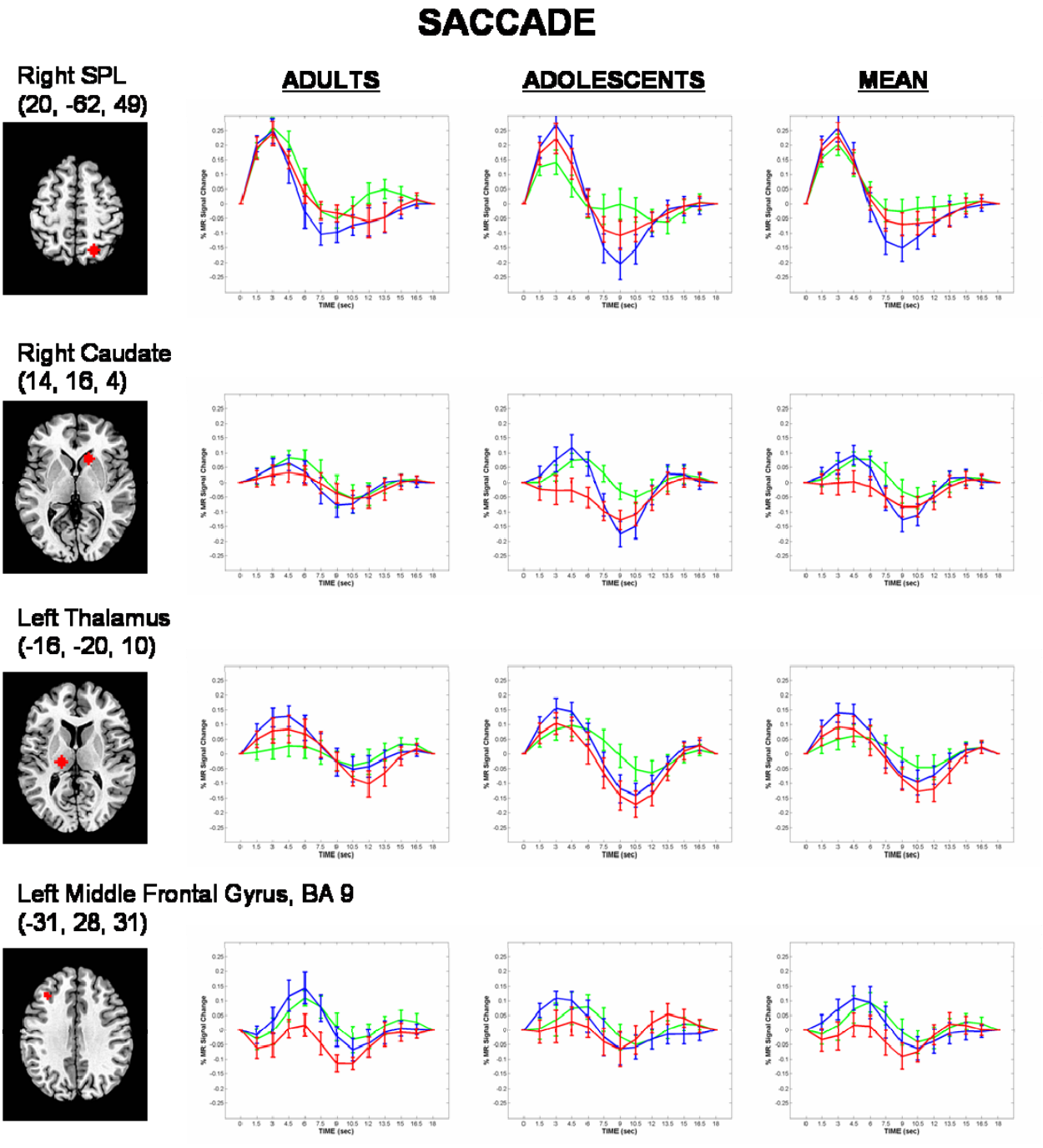

Figure 44. Saccade Response Epoch: Additional oculomotor control-related brain ROI demonstrating significant main effects of valence and/or valence by time interactions.

The hemodynamic time courses are plotted for adults (left column) and adolescents (middle column) separately. Additionally, the adolescent and adult responses were averaged and plotted in the right column. For each plot, green lines = reward trial response, red lines = punishment trial response, and blue lines = neutral trial response. Abbreviations: SPL = superior parietal lobule. Error bars = +/-1 S.E.M.

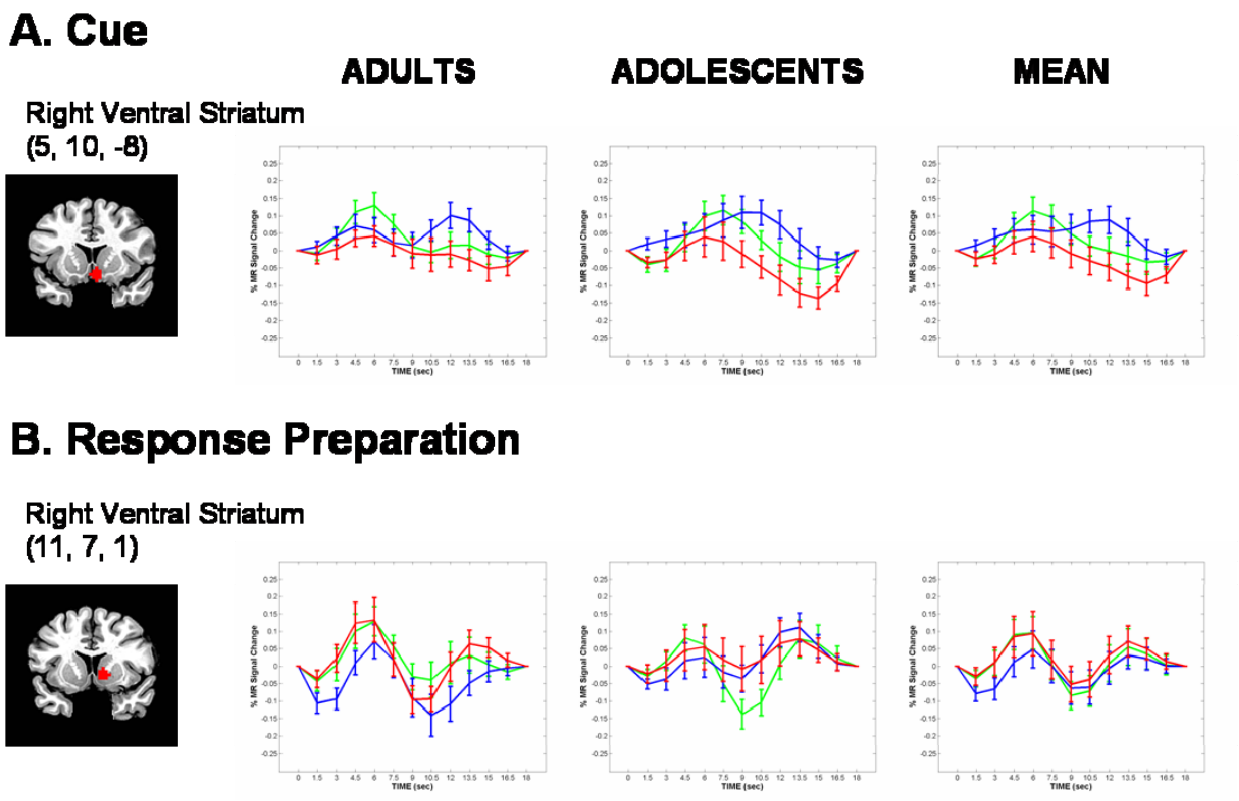

Figure 45. Time courses from ventral striatum during cue (A) and preparatory period (B).

The hemodynamic time courses are plotted for adults (left column) and adolescents (middle column) separately. Additionally, the adolescent and adult responses were averaged and plotted in the right column. For each plot, green lines = reward trial response, red lines = punishment trial response, and blue lines = neutral trial response. Error bars = +/-1 S.E.M.

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