Abstract

Title of dissertation: REWARD MODULATION OF INHIBITORY
                          CONTROL DURING ADOLESCENCE: AN
                          AGE RELATED COMPARISON OF
                          BEHAVIOR AND NEURAL FUNCTION

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The developmental period of adolescence is distinguished by a transition from the dependent, family-oriented state of childhood to the autonomous, peer-oriented state of adulthood. Related to this transition is a distinct behavioral profile that includes high rates of exploration, novelty-seeking, and sensation-seeking. While this adolescent behavioral profile generally aids in the transition to autonomy, it comes at a cost and is often related to excessive risk-taking behavior.

Current models attribute the adolescent behavioral profile to a developmental discordance between highly sensitive *reward-related processes* and immature *inhibitory control processes.* Specifically, reward-related processes appear to develop in a curvilinear manner characterized by a heightened sensitivity to reward that peaks during adolescence. On the other hand, inhibitory processes show a protracted linear developmental trajectory that begins in childhood and continues gradually throughout adolescence. Thus, the unique developmental trajectories of these two sets of processes

leave the adolescent with highly sensitive, reward-driven processes that can only be moderately regulated by gradually developing inhibitory processes.

Despite the usefulness of these models of adolescent behavior, they remain incompletely supported by data, as few studies specifically examine the interaction between reward-related and inhibitory processing. The current study addresses this particular gap in the adolescent neural development literature by administering a reward-modified inhibitory control task to children, adolescents, and young adults during functional neuroimaging.

Three key findings emerged from the current study. First, adolescents showed greater inhibition-related neural responses than both adults and children when potential monetary reward was available. Second, adolescents reliably showed greater striatal recruitment with reward than both adults and children. These differences in striatal response occurred as all three age groups showed significant reward-related behavioral improvements. Third, when reward was not present, adolescents and children showed deficient inhibitory behavior relative to adults.

Findings from this study support models proposing interactive relationships between heightened adolescent sensitivity to reward and protracted development of inhibitory control. Additionally, the current findings expand these models by suggesting heightened adolescent sensitivity to reward may facilitate developmentally inefficient inhibitory control processes in a bottom-up manner.

REWARD MODULATION OF INHIBITORY CONTROL DURING
ADOLESCENCE: AN AGE RELATED COMPARISON OF BEHAVIOR AND
NEURAL FUNCTION

By

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Chapter 1: General overview

The developmental period of adolescence is distinguished by the transition from a dependent, family-oriented state in childhood to an autonomous, peer-oriented state in adulthood. This fundamental shift is accompanied by refinements in the cognitive, emotional and social skills that facilitate exploratory, novelty-seeking, and sensation-seeking behaviors (Dahl, 2004; Spear, 2000). While this adolescent behavioral profile generally aids in the transition to autonomy, it comes at a cost and is often related to excessive risk-taking behavior. Some of these risk-taking behaviors are seen in the form of high rates of substance use/abuse, unsafe sexual practices, and reckless driving (Eaton, Kinchen, Ross, Hawkins, & Lowery, 2006; Johnston, O'Malley, Bachman, & Schulenberg, 2006; Rohde, Lewinsohn, Kahler, Seeley, & Brown, 2001).

Current models attribute the adolescent behavioral profile to a developmental discordance between highly sensitive *reward-related processes* and immature *inhibitory control processes* (Casey, Jones, & Hare, 2008; Ernst & Fudge, 2009; Hardin & Ernst, 2009; Steinberg, 2008). Reward-related processes are processes involved in the response to positive salient outcomes and the motivation to achieve these outcomes. These processes appear to develop in a curvilinear manner characterized by a heightened sensitivity to reward that peaks during adolescence (see Ernst & Spear, 2009). *Inhibitory control* processes are processes involved in the ability to suppress behavior that is prepotent, over-learned, or irrelevant (Aron, 2007; Curtis & D'Esposito, 2008; Nigg, 2000). Inhibitory processes show a protracted linear developmental trajectory that begins in childhood and continues throughout adolescence (see Casey, Getz, & Galvan, 2008).

Thus, the unique developmental trajectories of these two sets of processes leave the adolescent with highly sensitive, reward-driven processes that can only be moderately regulated by gradually developing inhibitory processes.

These models of adolescent behavior, however, remain incompletely supported by data. When examined in isolation, reward responses do appear exaggerated (Ernst et al., 2005; Galvan et al., 2006), and inhibitory control processes do appear immature during adolescence (Durston et al., 2002; Rubia et al., 2006). However, at a neural-systems level, few studies examine the interactions between reward-related and inhibitory processing. Given how relevant these interactions are for understanding adolescent deportment, the current study addresses the need for such data.

The current study addresses this particular gap in the adolescent neural development literature by administering a reward-modified inhibitory control task to children, adolescents, and young adults during functional neuroimaging. Findings from this study will provide information on the neural interactions between reward-related and inhibitory control systems during three distinct developmental periods. Given the proposed relationship between reward-related and inhibitory processes during adolescence, the results from this developmental period will be particularly pertinent.

Chapter 2: Literature review

Broadly speaking, adolescence is a developmental period of transition. During the relatively short period that roughly spans the teenage years, the highly dependent, family-oriented state of childhood gives way to the autonomous, peer-oriented state of adulthood. Related to this transition is a very distinct behavioral profile that includes high rates of exploration, novelty-seeking, and sensation-seeking. While this type of behavior is observable at all ages, during adolescence it reaches a peak and is more prevalent than at any other point in the lifespan. For example, a recently conducted, large (N=935), cross-sectional study of individuals between the ages of 10 and 30 years, demonstrates that adolescents show greater reward-sensitive (Cauffman et al., 2010; Steinberg et al., 2009) and sensation-seeking behavior (Steinberg et al., 2008) than both children and adults on both behavioral and self-report measures (Steinberg, 2008b).

This type of reward centered behavioral profile likely aids adolescents as they navigate their increasingly complex environments, and likely facilitates the transition to adult autonomy (Dahl, 2004; Spear, 2000). However, while this behavioral profile is generally beneficial, it can come at a cost by facilitating excessive risk-taking behavior. For example, adolescence is a time of disproportionate increases in many high-risk behaviors such as reckless driving (National research Council, 2007; Eaton et al., 2006), unsafe sexual practice (Eaton et al., 2006; Finer & Henshaw, 2006), and both violent and nonviolent crime (Piquero et al., 2003). Similarly, adolescents are more likely than children and adults to engage in illicit drug use (Eaton et al., 2006; Substance Abuse and Mental Health Services, 2007), and adolescence is a period of disproportionate increases in the rates of diagnosed substance use/abuse disorders (Rhode et al., 2001). These high-

risk behaviors also likely contribute to the disproportionately high adolescent rates of attempted suicide (Moscicki, 2001). Not only do these high-risk behaviors create a large public health concern, but they also contribute to an unfortunate paradox of adolescence. Despite adolescence being one of the most physically healthy periods of life, mortality rates show a marked increase during adolescence. While adolescents demonstrate similar abilities as adults to judge, estimate, and perceive vulnerability to risk (Fischoff et al., 2000; Millstein & Halpern-Felsher, 2002; Reyna & Farley, 2006), risk-taking is a primary contributor to markedly increased adolescent mortality rates. For example, approximately 70% of adolescent deaths result from high-risk behaviors related to motor vehicle accidents, homicides, unintentional (accidental) injury, and suicide (Eaton et al., 2006).

Two specific questions are fundamental for a thorough understanding of adolescent risk-taking (Steinberg, 2008). First, why does risk-taking increase between childhood and adolescence? Second, why does risk-taking then decrease between adolescence and adulthood? The recent advent of safe, readily available neuroimaging techniques, such as magnetic resonance imaging (MRI), have lead to brain level clues about these questions, and have lead to the development of *duel-system* models of adolescent risk-taking (Casey et al., 2008; Ernst, Pine, & Hardin, 2006; Steinberg, 2008). According to these models, risk-taking during adolescence results from interactions between developmental changes occurring in two neurobiological systems. One system is involved in reward-related processing and includes primarily subcortical dopamine circuits. The second system is involved in cognitive control (specifically, inhibitory control) processes and includes regions of prefrontal and parietal cortices. The duel-

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system models hypothesize that adolescent risk-taking is stimulated by a dramatic increase in dopaminergic activity in the reward-related system that begins in early/mid adolescence. The increased dopaminergic activity in the reward-related system is thought to lead to increased reward seeking which manifests in increased risk-taking behavior. However, the rapid change in the reward-related system precedes the protracted, gradual development of the cognitive (inhibitory) control system, and the connections that exist between the inhibitory control system and the reward-related system. Thus, the temporal gap between early/mid adolescent arousal in the reward-related system and the immature inhibitory control system results in a period of heightened vulnerability for high levels of risk-taking (Figure 1).

The follow review sections will provide greater detail about these two systems. Specifically, the following will provide an overview of reward-related processes and the underlying neural substrates of these processes. Additionally, reward-related processes during typical adolescent development will be discussed. This will be followed by an overview of inhibitory control processes and the underlying neural systems, as well as the typical behavioral and neural development of these processes during adolescence.

Reward-related processes

Reward-related processes are processes involved in the response to positive salient outcomes and the motivation to achieve these outcomes. These processes appear to develop in a curvilinear manner, that is characterized by a heightened sensitivity to rewards that peaks during adolescence (see Ernst & Spear, 2009). This peak in neural-based sensitivity is thought to facilitate reward- and sensation-seeking behavior. These behaviors are believed to be highly beneficial as adolescents explore their environment

and transition to independent being. However, these behaviors may also facilitate high-risk behaviors that are detrimental.

Reward-related neural circuitry

From a neuroscience perspective, the neural pathways involved in reward processing are perhaps some of the best delineated neural networks outside of those underlying basic sensory processing. Pathways supporting reward-related processing comprise primarily subcortical structures and dopaminergic projections to medial and orbital regions of the frontal cortex (Rolls, 2004; Schultz, 2000; Tobler, Fiorillo, & Schultz, 2005). More specifically, the receipt of rewarding outcomes typically involves the striatum (Delgado, Nystrom, Fissell, Noll, & Fiez, 2000; Elliott, Newman, Longe, & Deakin, 2003; Ernst et al., 2005; Seymour, Daw, Dayan, Singer, & Dolan, 2007). The striatum is composed of the caudate nucleus and the putamen, and can be segregated according to the topography of inputs from limbic, association, and motor-related regions (Ernst & Fudge, 2009). In general, the ventral striatum receives projections from the amygdala and cortical regions directly influenced by the amygdala, while the dorsolateral striatum receives inputs from sensorimotor regions, and the central striatum receives projections from associative (or "cognitive-related") regions (Ernst & Fudge, 2009).

In addition to the striatum, reward-related processes also recruit some frontal cortex regions. For example, the medial prefrontal cortex (mPFC) appears to track rewarding monetary outcomes (Knutson, Fong, Bennett, Adams, & Hommer, 2003), and also responds more strongly to positive than negative monetary incentive (Knutson et al., 2003). The orbitofrontal cortex (OFC) is involved in the representation of stimulus-reward value (Elliott et al., 2003; Gottfried, O'Doherty, & Dolan, 2003; O'Doherty,

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Kringelbach, Rolls, Hornak, & Andrews, 2001), and contributes to updating reward

values as they change with time (O'Doherty, Critchley, Deichmann, & Dolan, 2003;

O'Doherty, Rolls, Francis, Bowtell, & McGlone, 2001).

Adolescent reward sensitivity

Neurodevelopmental studies of reward-related processing conducted with

typically developing children and adolescents implicate recruitment of similar reward-

processing pathways as adults, and generally support heightened sensitivity to reward

during adolescence. For example, during monetary-based decision making, healthy

adolescents show striatal recruitment in response to monetary gains (May et al., 2004).

This finding matches that reported for healthy adults performing the same task (Delgado

et al., 2000), suggesting adolescents and adults recruit similar reward-related pathways.

While the pathways involved in reward-related processing appear similar for adults and

adolescents, the extent of neural recruitment appears to differ between age groups.

Specifically, striatal response to monetary gains during a decision-making task is reported

to be stronger for adolescents compared to adults (Ernst et al., 2005). Similarly, a

heightened striatal response to monetary reward is also reported when adolescents are

compared to both young children and adults during a delayed response task (Galvan et

al., 2006). However, some discrepancies among these findings do exist, with at least one

developmental neuroimaging study failing to detect striatal hyper-response in adolescents

during reward-related processing (Bjork et al., 2004). This particular study reported

greater striatal recruitment for adults than adolescents during the anticipation of a

potential reward (Bjork et al., 2004). The lack of an increased striatal response by

adolescents in this specific study led to the hypothesis of a hypo-functional reward

system in adolescence that requires extra stimulation to be maintained at a homeostatic level. An important difference between the studies reporting heightened striatal response and the one reporting striatal hypo-response in adolescents concerns the specific reward-related process under scrutiny, and may result from methodological differences such as the design of the specific paradigm used during neuroimaging.

While the current study will focus primarily on the reward-related role of the striatum, it is necessary to note that age-related differences in neural recruitment during the receipt of a reward are also reported in regions of the prefrontal cortex (PFC). Specifically, adolescents (relative to adults) show weaker dorsolateral PFC (DLPFC) recruitment (Ernst et al., 2005), and a more diffuse pattern of activation in the orbital frontal cortex when receiving a monetary reward (Galvan et al., 2006). Similarly, when adolescents make risky decisions that could lead to a large reward, they show less recruitment of the ventrolateral PFC than adults (Eshel, Nelson, Blair, Pine, & Ernst, 2007). This pattern of reduced PFC activation for adolescents relative to adults may suggest less efficient top-down cognitive control when adolescents are receiving a reward and showing highly appetitive behavior.

As one caveat to findings of adolescent differences in reward-related neural response, it is necessary to point out that studies of adolescent reward response typically utilize a monetary reward/incentive. This approach raises a number of questions when considering reported adolescent changes in reward-related neural recruitment. Particularly, this approach creates some difficulty in discerning whether these neural responses during adolescence are the result of increased reward sensitivity and motivation to acquire reward, or if the increased responses are the result of changes in the

salience of the reward (monetary) value. Future work focusing specifically on this question, and possibly utilizing additional types of rewarding stimuli will be necessary to help clarify this issue.

Inhibitory control processes

Human behavior is flexible and goal directed. As such, *inhibitory control* processes are processes involved in the ability to suppress behavior that is prepotent, over-learned, or irrelevant (Aron, 2007; Curtis & D'Esposito, 2008; Nigg, 2000). Inhibitory control is commonly conceptualized as one of two possible sub-types, cognitive or motor (Aron, 2007; Harnishferger, 1995; Nigg, 2000). Cognitive inhibitory control involves the suppression of cognitive content or processes, such as those involved in unintentional thoughts (Harnishfeger 1995). Processes involved in motor inhibitory control are involved in controlling overt behaviors (e.g. motor responses, resisting temptations, delaying gratification), and are distinct from those involved in cognitive inhibition. The current review and study will concentrate on motor inhibitory control rather than cognitive.

Behavioral measures of inhibitory control

Experimental paradigms probing inhibitory control processes commonly include the antisaccade eye movement, go/no-go, and stop signal tasks. These paradigms employ the common strategy of pitting suppression of a naturally prepotent or over-learned response against the required action of an unnatural or novel response. The inhibitory demands of these paradigms are exceptionally high, and they are frequently employed in neuroimaging setting to probe the neural circuitry underlying inhibitory behavior. An

antisaccade paradigm is utilized in the current study. However, the following discussion will also refer to the go/no-go and stop-signal paradigms, as findings that result from these paradigms inform our current knowledge of inhibitory-related processes.

Behavioral responses during the antisaccade paradigm are made by generating saccade eye movements either towards or away from a target that appears in the visual periphery. Saccades are rapid ballistic eye movements that shift one's gaze to an image of interest (target), and bring that image to the center of the fovea (the maximum area of acuity in the eye). In the traditional antisaccade paradigm (Hallett, 1978), a gaze shift is required towards the periphery opposite the target (see Figure 2). This look towards the opposite periphery is referred to as an *antisaccade*. The antisaccade response requires two steps. First, the reflexive, prepotent tendency to saccade towards the target must be inhibited. Then, a saccade to the opposite periphery must be generated. For comparison/control purposes, most antisaccade paradigms also include prosaccade trials where the task is simply to saccade towards the target. The gaze shift towards the peripheral target is referred to as a *prosaccade*, and is primarily a reflexive/prepotent response.

Antisaccade accuracy (number or percent of successful antisaccades) and latency represent two common behavioral metrics of inhibitory control. Comparison of antisaccade to prosaccade behavior consistently reveals more antisaccade than prosaccade errors (Munoz & Everling, 2004). Antisaccade errors are characterized by small amplitude saccades generated toward the target, and reflect inhibitory control failure (Curtis & D'Esposito, in press). The time to initiate an antisaccade (antisaccade latency) is typically longer than the time to initiate a prosaccade (Fischer, Biscaldi, &

Gezeck, 1997; Munoz & Everling, 2004). The longer latency to initiate an antisaccade results from the extra time required to inhibit the prepotent prosaccade, plus the time required to generate a saccade to the opposite periphery (Fischer et al., 1997; Munoz & Everling, 2004). Accuracy is considered a metric of *effectiveness*, and reflects the degree to which inhibitory processes are intact (Derakshan, Ansari, Hansard, Shoker, & Eysenck, in press; Eysenck, Derakshan, Santos, & Calvo, 2007). Antisaccade latency is considered a metric of *efficiency*, or how well inhibitory control processes function. Typically, the shorter the latency of an antisaccade the more efficient the underlying inhibitory control processes function (Derakshan et al., in press; Eysenck et al., 2007). Of particular note, both antisaccade accuracy and latency are highly sensitive to task timing and paradigm design (see Munoz & Everling, 2004). This is particularly true for manipulations of the time duration between the offset of the central fixation point and the onset of the peripheral target. For this reason, it is necessary to use caution when making specific, direct comparisons of these parameters across studies.

Behavioral development of inhibitory control

Available data concerning the behavioral development of inhibitory performance suggests a steady improvement of inhibitory behavior throughout childhood and adolescence. Studies employing age appropriate versions of many traditional inhibitory control paradigms (e.g., go/no-go) implicate a period of rapid inhibitory improvement that typically occurs in childhood between the ages of three and five years (Diamond & Taylor, 1996; Gerstadt, Hong, & Diamond, 1994; Jones, Rothbart, & Posner, 2003; Simpson & Riggs, 2007). During this age period, children can verbalize and conceptually understand inhibition-related rules, but have difficulty translating their understanding into

efficient inhibitory behavior (Bell & Livesey, 1985; Dowsett & Livesey, 2000; Livesey & Morgan, 1991; Zelazo, Frye, & Rapus, 1996). The ability of children to comprehend inhibitory rules coupled with inefficient inhibitory behavior suggests that early inhibitory performance deficits result from immature inhibitory control processes, rather than immature language ability/comprehension – related processes.

A close examination of the available antisaccade inhibition studies focusing on development suggest that inhibitory behavior continues to improve throughout childhood and adolescents. Table 1 provides a brief overview of these studies and brings to light a number of key findings. First, overview of the accuracy results reveals no age-related difference in prosaccade performance. This is a very important finding in that it suggests the processes required for generating saccade eye movements are in place by time of the earliest study age (4 years). Because the processes involved in generating saccades are in place, accuracy differences observed with antisaccades can be attributed to inhibitory processes. An overview of the accuracy results also consistently reveals decreasing antisaccade errors rates with age. Specifically, the age-related increase in antisaccade accuracy appears to begin in late childhood, and end by late adolescence or early 20s. Together, this overview of pro and antisaccade accuracy are consistent with hypotheses that inhibitory control processes are functional during childhood, but continue a gradual developmental trajectory that spans adolescence.

As apparent in Table 1, most of the reported findings from antisaccade development studies occur with latency variables. This is a critical observation in that it suggests most of the age-related developments taking place during late childhood and through adolescence occurs in the functional efficiency of inhibitory processes.

Additionally, the findings point to a pattern of rapid inhibitory efficiency increases occurring roughly during mid adolescence. Two important implications result from these latency-based findings. First, when translating these behavioral results to a neural level, one would expect the latency increases to be reflected more in neural function and connectivity between regions, and less in neural structure (which would presumably be reflected more by accuracy findings). Second, the mid-adolescent age range when most efficiency increases are occurring approximately coincides with the age-range when heightened reward sensitivity begins to decline. It should also be noted that the general direction of these latency findings appears robust despite methodological differences across studies (which appear to create uniform shifts in the latencies).

Neural circuitry of inhibitory control

Converging evidence from both human and non-human primate studies implicate prefrontal cortical regions in inhibitory processes. This is particularly true for inferior fontal cortex (IFG), which is recruited during a number of inhibition paradigms (Curtis & D'Esposito, 2008; Ridderinkhof, van den Wildenberg, Segalowitz, & Carter, 2004). Specific to the antisaccade paradigm, additionally reported regions include the frontal eye fields (FEF), and supplementary eye fields (SEF) (Munoz & Everling, 2004).

Recruitment of the IFG occurs during both motor (i.e., go/no-go and stop-signal) and ocular (i.e. antisaccade) response paradigms, and is typically right lateralized (Aron, Robbins, & Poldrack, 2004). For example, inhibitory deficits during a stop-signal paradigm are reported for adult patients with right IFG (rIFG) damage (Aron, Fletcher, Bullmore, Sahakian, & Robbins, 2003). Additionally, when rIFG function is disrupted by transcranial magnetic stimulation, inhibitory behavior during the stop-signal paradigm

is affected Chambers et al., 2006). Functional neuroimaging studies conducted with adult subjects also provide evidence of rIFG involvement in inhibitory control processes. For example, rIFG responses are greater during the no-go (inhibition) trials of a go/no-go paradigm than during go trials (Garavan, Ross, & Stein, 1999; Konishi et al., 1999; Liddle, Kiehl, & Smith, 2001). Likewise, "stop" trials during a stop-signal paradigm correspond with greater rIFG recruitment than "go" (Aron & Poldrack, 2006; Rubia, Smith, Brammer, & Taylor, 2003). Recruitment of the rIFG is also reported during antisaccade paradigms, though this is reported less consistently than with go/no-go or stop-signal paradigms. However, the inconsistent rIFG response during antisaccade paradigms appears to be a methodological artifact that is dependent on the amount of time allotted for inhibitory preparation (Chikazoe, Konishi, Asari, Jimura, & Miyashita, 2007).

Electrophysiological recording studies conducted with non-human primates provide a wealth of information on the neural mechanism underlying antisaccade inhibition. Two specific types of neurons are active in the FEF and SEF during antisaccade inhibition. These include: "saccade" neurons which show increased firing rates just prior to a saccade, and result in the generation of a saccade when; and "fixation" neurons that are active when eye gaze is fixed in a stationary position (see (Schall, 2002). During an antiasaccade paradigm, saccade and fixation neuron firing rates are modulated in a reciprocal manner (Munoz & Everling, 2004). When correct antisaccades are generated, firings of fixation neurons are greater than those of saccade neurons. When correct prosaccades or incorrect antisaccades (prosaccades toward the response target) are generated, firings of saccade neurons are greater than activity in

fixation neurons. These differences in neural activity are observed in the FEF during

saccade preparation, and predict antisaccade errors (Munoz & Everling, 2004).

Additionally, SEF neurons show increased firing rates during the preparation of

antisaccades, and likely contribute to the overall accumulation of net activity required for

antisaccade responses (Amador, Schlag-Rey, & Schlag, 2004; Schlag-Rey, Amador,

Sanchez, & Schlag, 1997).

　　　Functional neuroimaging studies conducted with healthy adults consistently report

recruitment of FEF and SEF in antisaccade inhibition. In addition to these two regions,

early neuroimaging studies using block designs also reported a number of additional

cortical and subcortical regions (e.g., O'Driscoll et al., 1995). However, this additional

recruitment likely resulted from the inability of block designs to separate inhibitory

preparation from motor responses (Hutton & Ettinger, 2006; Munoz & Everling, 2004).

Recent event-related fMRI studies that can better isolate inhibitory responses, robustly

demonstrate greater FEF responses during antisaccade than prosaccade preparation

(Brown, Vilis, & Everling, 2007; Curtis & D'Esposito, 2003; DeSouza, Menon, &

Everling, 2003; Ford, Goltz, Brown, & Everling, 2005).

　　　Neural development of inhibitory control

　　　The behavioral development of inhibitory control that takes place during

childhood and adolescence appears to parallel neural maturation that also occurs during

this time (Bjorklund & Harnishferger, 1995; Dempster, 1992; Durston & Casey, 2006).

This is particularly true during late childhood and adolescence, as both periods involve

ongoing structural and functional development in frontal brain regions (see Casey, Galvan, & Hare, 2005; Durston & Casey, 2006; Paus, 2005).

Structural neuroimaging studies have been conducted to track the anatomical course of normal brain development. This work demonstrates increasing brain volume that occurs over the first few years of life that is followed by relative stability throughout mid and late childhood (Caviness, Kennedy, Richelme, Rademacher, & Filipek, 1996; Giedd et al., 1999; Giedd et al., 1996). However, longitudinal structural neuroimaging studies indicate different developmental trajectories that exist across brain regions (e.g. Giedd, 2004). Specifically, developmental patterns are characterized by an initial increase of grey matter volume, followed by a subsequent decrease. These patterns first occur in sensori-motor areas and end in PFC (Giedd, 2004; Gogtay et al., 2004; Lenroot & Giedd, 2006). The protracted development of PFC (including areas implicated in inhibitory control) grey matter volume begins during late childhood and continues throughout adolescence and into early adulthood. Simultaneously, white matter volume continues to increase through childhood and adolescence in a pattern that also begins caudally and moves rostrally with age (Durston & Casey, 2006; Lenroot & Giedd, 2006). Increases in white matter volume reflect increased neuronal myelination, and correspond with the improved cognitive efficiency occurring during adolescence (Casey et al., 2005; Durston & Casey, 2006; Paus, 2005).

Developmental differences in neural function are also reported when performing inhibitory control paradigms. For example, during the go/no-go and stop signal paradigms children and adolescents show greater rIFG responses during successful inhibition than unsuccessful inhibition (Booth et al., 2004; Durston et al., 2002), with the

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magnitude of the inhibition responses showing linear increases with both age (Rubia et al., 2001; Rubia, Smith, Taylor, & Brammer, 2007; Tamm, Menon, & Reiss, 2002) and performance (Booth et al., 2004). Despite indications that developmental differences do exist in rIFG function during inhibition, inconsistencies about the specific directionality of the differences arise across studies. For instance, some developmental studies report greater inhibition-related rIFG responses for adults relative to children and adolescents (Bunge, Dudukovic, Thomason, Vaidya, & Gabrieli, 2002; Rubia et al., 2000; Rubia et al., 2007; Tamm et al., 2002), while others report greater inhibition-related rIFG responses for children and adolescents relative to adults (Booth et al., 2003; Durston et al., 2002). Methodological differences may underlie the inconsistencies across these studies, as many of these works used slightly different task paradigms and different imaging techniques. Many early developmental neuroimaging studies used a block design approach. Parsing successfully inhibited trials from unsuccessfully inhibited trials is difficult in block designed studies, leading to findings that combined both trials types. Recently conducted studies that use event-related approaches and are able to parse successful from unsuccessful trials, and appear somewhat consistent in indicating greater inhibition-related rIFG responses for adults relative to children and adolescents (Rubia et al., 2007).

Overview of the current study

Directly relevant to questions concerning the interaction between reward-related processes and inhibitory control, recent behavioral studies have used modified antisaccade paradigms to examine the modulation of inhibitory control by potential monetary incentives. These works consistently report better inhibition with the potential

for a monetary incentive than without the potential for incentive (Blaukopf &

DiGirolamo, 2005; Duka & Lupp, 1997; Hardin, Schroth, Pine, & Ernst, 2007; Jazbec et

al., 2006). The two developmental studies that have used a modified antisaccade

approach report more antisaccade errors for adolescents than adults (Hardin et al., 2007;

Jazbec et al., 2006). Despite demonstrating a developmental difference, both adults and

adolescents exhibited better inhibition when there was potential for an incentive than

when there was no potential for an incentive. The latency to correctly inhibited

antisaccades when there was potential for incentive was similar for adults and

adolescents, suggesting adolescents performed with adult-like efficiency in the presence

of potential incentive (Hardin et al., 2007). The findings from these modified antisaccade

studies not only support models of immature inhibitory control and heightened reward

sensitivity during adolescence, they also provide a valid approach to further study the

interaction between reward and inhibitory control processes during adolescence.

Purpose of the current study

As previously discussed, models of adolescent behavior propose an imbalance

between the developmental trajectories of reward-related and inhibitory control

processes. While most evidence does point to the validity of these models, neuroimaging

evidence is scant. This is particularly true of neuroimaging studies that directly examine

the interaction between reward-related and inhibitory control processes, as no known

studies of this type have been conducted. Given this limitation, the purpose of the current

study is to directly explore the functional interaction between reward-related and

inhibitory control processes in children, adolescents, and young adults.

Overview of study design

Children, adolescents, and young adults performed a modified antisaccade
paradigm that included the potential to receive an incentive for correct saccade responses.
All age groups performed the paradigm during fMRI scanning. During each trial of the
paradigm, one of two possible cues ($, O) was presented in one of two possible font
colors. Dollar sign cues signaled the potential to either win or lose money for a correct or
incorrect saccade response. The open circle cue signaled no-potential to win or lose
money with a correct or incorrect saccade response. The cue color signaled to make
either a prosaccade or and antisaccade.

Both behavioral and neuroimaging data were collected throughout the paradigm.
Behavioral data consisted of response accuracy (percent of correct antisaccades and
prosaccades), and response latency. Antisaccade accuracy was considered a metric of the
effectiveness of inhibitory control. Latency to correct antisaccades was considered a
metric of the *efficiency* of inhibitory control. Neuroimaging data was collected in an
event-related manner, and consisted of BOLD responses in each saccade (antisaccade and
prosaccade) and incentive (incentive and no-incentive) condition. Whole brain analyses
were conducted on the neuroimaging data, and were followed up by region of interest
(ROI) analyses conducted on functionally defined ROIs.

Behavioral hypotheses

A main effect of age group is expected for both antisaccade accuracy and latency.
Adults are expected to be most accurate and respond fastest, followed by adolescents,
then children. A main effect of reward is expected for both accuracy and latency.
Accuracy is expected to be higher, and latency shorter for incentive compared to no-

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incentive trials. Adolescents are expected to show an equal or greater reaction time difference between incentive and no-incentive responses compared to adults. Meanwhile, both adolescents and adults are expected to show a greater reaction time difference between incentive and no-incentive responses compared to children.

Neuroimaging hypotheses

Adolescents are expected to show a greater response in striatum during incentive antisaccades compared to both adults and children. Greater rIFG recruitment during incentive antisaccades relative to no-incentive antisaccades is expected for all age groups. However, the difference in rIFG recruitment between incentive and no-incentive antisaccades is expected to be largest for adolescents, followed by adults, then children.

Neural responses during correctly inhibited antisaccades in the no-incentive condition are expected to be consistent with those reported by traditional antisaccade studies. During no-incentive antisaccades, adults are expected to show a greater eye field and rIFG response than both adolescent and children. Meanwhile, adolescents are expected to show are greater eye field and rIFG response during no-incentive antisaccades than children.

Chapter 3: Methods

Participants

Participants consisted 15 children age 9-11years (*M*=10.23, 8 female); 15 adolescents age 14-16 years (*M*=15.27, 7 female); and 15 young adults age 20-25 (*M*=21.83, 7 female).

Participant recruitment was conducted through the Emotional Development and Affective Neuroscience Branch (EDAN) at the National Institute of Mental Health (NIMH). EDAN recruitment procedures include local advertisements and recruitment through the National Institutes of Health (NIH) office of normal volunteers. Individuals recruited through EDAN underwent a standard screening procedure that included a medical history, psychiatric history, and physical examination. Data from the screening procedures was used to determine study eligibility, however it was not used for any hypothesis related analyses. Participation was limited to children aged 9-11 years, adolescents age 14-16 years, and young adults age 20-25 years. Based on standard EDAN procedures, individuals were excluded from participation for the following reasons: 1) history or current diagnosis of any axis I psychiatric disorder; 2) current or history of drug abuse; 3) chronic or severe acute medical illness; 4) history of brain abnormalities, cerebrovascular disease, infectious disease, any other neurological disease, or history of head trauma (defined as loss of consciousness > 3 min); 5) IQ lower than 70; 6) metal or electronic objects in the body; 7) claustrophobia; or 8) pregnancy.

Participant visits began with a discussion of the study procedures and the consenting process. For child and adolescent participants, the consent procedure included the participant's parents. Consents were signed by the parents of child and adolescent participants, and by the participants themselves for young adults. An age-appropriate assent form was discussed with, and signed by child and adolescent participants. The University of Maryland Institutional Review Board, and the National Institute of Mental Health Institutional Review Board approved all consent/assent forms and study procedures.

Following consent procedures, participants completed a battery of screening procedures. These procedures included a demographic information questionnaire, a physical examination, a psychiatric interview, and a neuropsychological examination. EDAN staff members performed all screening procedures. A licensed clinician conducted the psychiatric interviews, and a medical doctor conducted the physical examinations. Following the screening procedures, participants were trained on the saccade reward task (SRT). The training included a minimum of one full block of practice, and was repeated until participants fully understood the task. Participants that met all eligibility requirements were then acclimated to the magnetic resonance (MR) environment by practicing in a mock fMRI scanner.

Following the evaluation and training procedures, participants returned on a second day to undergo fMRI scanning. All scanning was completed at the National Institutes of Health medical center. Prior to scanning participants completed a screening form to ensure their body was free of metallic objects. Additionally, female participants

were asked to provide a serum pregnancy screen. A brief training session was conducted to remind participants of the SRT rules, and then participants completed the task during fMRI scanning.

Measures

Saccade Reward Task (SRT)

The SRT (Figure 3) was designed to assess inhibitory control by contrasting performance and processes during antisaccade generation with those during prosaccade generation. The SRT was modified from a standard antisaccade task (Hallet, 1978; Munoz, 2004) by including two explicitly presented reward conditions (Incentive, No-incentive). The task was similar to the modified antisaccade task used in previous behavioral studies (Hardin et al., 2007; Jazbec et al., 2006; Jazbec, McClure, Hardin, Pine, & Ernst, 2005). Results from the SRT provide insight specifically into antisaccade inhibition in the context of a monetary reward.

Task trials were comprised of three phases: (1) the *cue* phase informed the participant of the incentive condition;(2) the *target* phase signaled the participant to execute a saccade response; (3) the *feedback* phase provided the location of the correct response. The feedback phase was followed by a fixation inter-trial interval (ITI). Participants were instructed to fixate the cue during the cue phase, to respond with the proper eye movement during the target phase, and to fixate the correct location feedback during the feedback phase.

Each task trial began with the presentation of one of two possible cues. The cue was located at the center of a computer screen and subtended 1°. Participants were instructed to fixate the cue until it disappeared. The cue signaled one of two conditions:

(1) Incentive; (2) No-incentive. The Incentive condition was cued by a "$", while the No-incentive condition was cued by a "O". In the Incentive condition, participants could win $2.00 for a correct saccade, but lose $0.50 for an incorrect saccade. In the No-incentive condition participants did not win or lose money for their responses. The cues were presented in either yellow or pink font. The color signaled the type of saccade (prosaccade or antisaccade) required for that trial. On prosaccade trials, participants were instructed to look at the suddenly appearing peripheral target. On antisaccade trials, participants were instructed to look to the opposite mirror location of the suddenly appearing target. The color assignment to pro- or anti- saccade was counter-balanced across subjects. Participants were informed of the meaning of the color prior to the task onset, and were trained on the task before scanning. Participants were also reminded of the pairing prior to each task run. The cue duration was jittered between 1500-2500ms to minimize time-locked participant responses, and also to maximize detection of the hemodynamic response corresponding with preparation to inhibit prepotent saccade responses.

Following the cue presentation the reward cue was replaced by a laterally appearing target stimulus. The target stimulus remained on the screen for 1500ms, and consisted of a "*". The target was presented in white font and subtended 1°. The target appeared at the vertical center and 6° to the left or right horizon of the screen center and was immediately followed by a feedback symbol appearing where the subject should be looking for correct response. The feedback symbol was a square presented in white font that remained on the screen for 1000ms. A fixation symbol "+" then reappeared in the

center of the screen to reorient the subject to the center location for the duration of the inter-trial intervals (ITI). ITIs were of random duration between 0 – 6000ms.

The SRT included 192 trials total and was presented in eight runs of 24 trials. These trials comprised 128 antisaccades (64 Incentive, 64 No-incentive), and 64 prosaccades (32 Incentive, 32 No-incentive). To compensate for the typically higher error rate for antisaccades than prosaccades, the task included twice the number of antisaccade trials than prosaccade trials because. This was done to ensure an adequate number of correct antisaccade trials and to avoid under-powering of the antisaccade condition. Total task duration was 20 minutes. At the end of each run, participants were shown the total amount of money won during that run. Subjects were informed they would receive the cumulative amount of money won during the task. During fMRI scanning, the SRT was presented via a Silent Vision SV-7021 Fiber Optic Visual System (Avotec Inc., Stuart, Florida, USA). This device projected video and computer based images via fiber optics from a computer located in the scanner control room to goggles located above the participants' eyes in the MRI scanner.

Eye movement recording

During fMRI scanning, saccade eye movements were continuously recorded with a Real Eye RE-4601 Imaging System (Avotec Inc., Stuart, FL, USA) at a 60Hz sampling rate. Recording and online monitoring of eye movements were conducted with an iViewX Eye Tracking System (SensoMotoric Instruments, Teltow, Germany). Each participant was calibrated using a nine point calibration prior to the task. The calibration was repeated between task runs if needed.

fMRI acquisition

Scanning was conducted on a 3 Tesla General Electric Signa scanner. Avotec Silent Vision Glasses (Stuart, FL) were used to present the task during scanning. Gradient echo planar (EPI) images were collected following sagittal localization and a manual shim procedure. EPI images consisted of a series of 30 interleaved 4 mm sagittal slices covering the whole brain and parallel to the AC-PC line. The fMRI sequence used echo planar single shot gradient echo T2 weighting. The imaging parameters included: 64 x 64 matrix; TR = 2500ms; TE = 23ms; FOV = 240mm; voxels were 3.75mm × 3.75mm × 4 mm. Following EPI acquisition, high resolution T1-weighted whole brain structural scans using a magnetization prepared gradient echo sequence (MPRAGE) were acquired. The parameters for these structural scans were 180 1.0 mm sagittal slices; FOV= 256 mm, NEX = 1, TR = 11.4 ms, TE = 4.4ms; matrix = 256 x 256; TI = 300ms, bandwidth 130 HZ/pixel = 33 kHz for 256 pixels. These high resolution structural scans were used for coregistration with functional scan data.

Analysis

Saccade eye movement analysis

Raw eye movement data was analyzed off-line with ILAB software (Gitelman, 2002) and in-house scripts written in Matlab6. Saccade eye movements were defined as movements with velocity greater than 30° per second that lasted for a minimum duration of 25ms. When determining correct and incorrect movements, only the first saccade following onset of the target stimulus was considered. For antisaccade trials, a _correct antisaccade_ response occurred when the first post-target saccade was made in the

direction opposite to the target. An *incorrect antisaccade* occurred when the first post-target saccade was made in the same direction as the target. For prosaccade trials, a *correct prosaccade* response occurred when the first post-target saccade was made in the same direction as the target. An *incorrect prosaccade* occurred when the first post-target saccade was made in the direction opposite to the target. Saccade variables of interest included accuracy and latency. Saccade *accuracy* was indexed as the percent of saccades directed to the correct location. Saccade *latency* was the elapsed time between target onset and the start of the first movement identified as a saccade. To ensure that only task-relevant saccades were considered, analyses were restricted to saccades that occurred 80-700ms after target onset. Analyses of accuracy and latency consisted of age-group by saccade-type by incentive-type repeated measures ANOVAs. Significant interactions were followed by *post hoc* pairwise analyses.

Imaging analysis

Reconstructed functional images were analyzed with Medx software to check for excessive motion. Data from participants moving more than 4mm in any plane was discarded. All subsequent analyses were conducted with SPM2 (Welcome Department of Neurology) and additional routines written in Matlab6. Data preprocessing included correction for slice sequence acquisition, motion correction, and spatial normalization to the Montreal Neurological Institute (MNI) T1-weighted template image supplied with SPM.

At the individual participant level, event-related response amplitudes were estimated using a General Linear Model (GLM) for each crossing of the saccade-type (antisaccade, prosaccade) by incentive-type (Incentive, No-incentive) factorial design.

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The waveform used to model each type of event-related response in the GLM was a rectangular pulse of the duration of the event convolved with the synthetic hemodynamic response function provided by SPM. Contrast images were generated for each participant using pairwise comparisons of the event-related BOLD responses across event types. Prior to group-level analysis, each contrast image was divided by the participant-specific voxel time series means. This yielded values proportional to percent fMRI signal change. These normalized contrast images were smoothed with an isotropic gaussian kernel (FWHM = 8mm) to mitigate any non-stationarity in spatial autocorrelation structure introduced by the previous step.

For all group-level analyses a random effects model was employed to permit population-level inferences (Holmes & Friston, 1998). The primary analyses were conducted at the whole brain level, $p<.05$ uncorrected. This liberal threshold was used primarily because of (1) the exploratory nature of the study, and (2) the relatively small size of the three age groups. A cluster size of 20 voxels was considered the minimum for significance. Additional follow-up analyses were conducted on functionally defined regions of interest (ROI). The functional ROIs consisted of 6mm spheres drawn around the peak voxel in regions showing significant responses at the whole brain level. Based on *a priori* evidence of their recruitment during reward processing and inhibitory control, the functional ROI analyses were restricted to responses that occurred in the: (1) bilateral striatum, (2) right inferior frontal gyrus (rIFG), and (3) bilateral frontal eye fields (FEF) and supplementary eye field (SEF) For each contrast in which a significant whole brain level response occurred in one of these regions, the mean BOLD response level was

extracted from a 6mm sphere around the peak voxel, and subjected to further analyses in SPSS 15.0.

The four events of interest in the current study included: (1) correct antisaccades in the Incentive condition; (2) correct antisaccades in the No-incentive condition; (3) correct prosaccades in the Incentive condition; and (4) correct prosaccades in the No-incentive condition. The events of interest spanned the duration of the cue and target phases. The outcome phase was coded as an event of no-interest. Finally, the implicit baseline consisted of all residual activity that was not coded as an event of interest or no-interest.

The primary study analyses were designed to isolate the interaction between reward and inhibitory processes. Isolation of this interaction was achieved in the contrast *Incentive (antisaccade vs. prosaccade) vs. No-incentive (antisaccade vs. prosaccade).* This contrast provided activations specific to inhibition in the Incentive condition, while controlling for activation specific to the No-incentive condition. Analyses were additionally conducted for the contrasts: (1) *Incentive (antisaccade vs. prosaccade),* which provided activations specific to inhibition in the incentive condition; and (2) *No-incentive (antisaccade vs. prosaccade),* which provided activations specific to inhibition during no-incentive trials. Given the incentive free nature of the no-incentive (antisaccade vs. prosaccade) contrast, this contrast is similar to those typically conducted to gage inhibition relevant activation during traditional antisaccade studies.

Chapter 4: Results

Behavioral performance

Accuracy

An age-group (Child, Adolescent, Yong Adult) by saccade-type (antisaccade, prosaccade) by incentive-type (Incentive, No-incentive) repeated measures ANOVA conducted on percent of correct saccade responses resulted in a significant main effect of age group, $F(1,42) = 4.13$, $p<.05$ (Table 2). Additionally, a significant main effect of incentive-type, $F(1,42) = 12.58$, $p<.001$ (Figure 4), and a significant main effect of saccade-type, $F(1,42) = 23.34$, $p<.001$, emerged. No interaction effects were present for percent of correct saccades.

Consistent with expectations, the main effect of saccade-type indicated better accuracy for prosaccade trials (M=70.7% SE=2.1%) than antisaccade trials (M=61.4% SE=1.6%). Likewise, the main effect of incentive-type indicated better accuracy for Incentive (M=69.8% SE=1.8%) than for No-incentive (M=62.3% SE=2.1%). The significant age-group effect was characterized by better accuracy for young adults relative to both children ($p<.05$) and adolescents ($p<.05$).

Latency

An age-group (Child, Adolescent, Young Adult) by saccade-type (antisaccade, prosaccade) by incentive-type (Incentive, No-incentive) repeated measures ANOVA conducted on the latency to correct saccades resulted in a significant main effect of saccade-type, $F(1,42) = 20.58$, $p<.001$, and a significant main effect of incentive-type,

$F(1,42) = 8.01$, $p<.01$ (Table 3) (Figure 5). Both main effects were consistent with expectations of faster latencies for prosaccade trials ($M=321.7$ms; $SE=22.63$ms) than antisaccade trials ($M=387.58$ms; $SE=28.86$ms), and for incentive trials ($M=345.27$ms $SE=24.36$ms) than no-incentive trials ($M=364.04$ms; $SE=25.86$ms). No significant group or interaction effects were present for latency of responses.

Neuroimaging results

Given the group differences that existed in saccade performance, it was necessary to inspect the number of events per condition that contributed to the neuroimaging analysis for each group.

No group differences existed in the number of individual events contributing to the Incentive prosaccade condition (children: $M=14.0$; adolescents: $M=18.4$; Adults: $M=18.6$). However, children ($M=13.4$) did have significantly fewer events contribute to the No-incentive prosaccade condition than young adults ($M=19.8$). Adolescents ($M=17.06$) did not differ from either children or young adults.

Children ($M=17.2$) had significantly fewer events contribute to the Incentive antisaccade condition that both adolescents ($M=25.6$) and young adults ($M=26.0$). Similarly, children ($M=16.8$) had significantly fewer events contribute to the No-incentive antisaccade condition than both adolescents ($M=23.4$) and young adults ($M=24.5$).

Whole brain analyses

The contrast *Incentive (antisaccade vs. prosaccade) vs. No-incentive (antisaccade vs. prosaccade)* provided activations specific to inhibition in the Incentive condition,

when controlling for activation specific to the No-incentive condition. Whole brain
analyses during this contrast yielded a number of significant responses when each age
group was examined independently, as well as when direct contrasts were conducted
between the age groups. Table 4 provides an overview of these significant responses for
each age group independently, and for each age group comparison. Specifically, Table 4
provides the size of the significant region of activation (k cluster), the peak T-value
occurring in that region, the Brodmann area in which the region can be found, and the
coordinates (x,y,z) of the voxel corresponding with the peak T-value. Of particular note
in Table 4, and consistent with expectations, the significant responses included greater
recruitment of the striatum (caudate head) for adolescents relative to adults, and greater
recruitment of the rIFG for adolescents relative to children.

The contrast [Incentive (antisaccade vs. prosaccade) vs. No-incentive (antisaccade
vs. prosaccade] was further deconstructed to better understand the contributing
components. Whole brain analysis of the contrast *Incentive (antisaccade-prosaccade)*
provided the regions showing significant responses during inhibition in the Incentive
condition. This contrast yielded a number of significant responses when each age group
was examined independently (relative to baseline), and also during direct comparisons
between age groups. Table 5 provides an overview of the significant whole brain
responses for each group independently, and for the comparisons between groups.
Relevant to the study hypotheses, the significant findings included greater recruitment of
striatum (caudate head and tail) for adolescents relative to adults but not children, and
greater recruitment of rIFG for adolescents relative to children but not adults. Adults also
showed greater recruitment of rIFG relative to children.

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A whole brain analysis of the *No-incentive (antisaccade vs. prosaccade)* contrast revealed the regions showing significant responses during inhibition in the No-incentive condition. Table 6 provides an overview of regions showing significant responses in each of the three groups independently (relative to baseline), and for the direct comparison between groups. While the significant responses in this contrasts included regions implicated in visual processing and motor control, no significant group differences existed in the regions that were directly hypotheses relevant (i.e. striatum, rIFG, eye fields).

Region of interest analyses

Unlike the whole brain analyses that consider the statistical significance of responses in voxels across the entire brain, region of interest (ROI) analyses are restricted to the voxels that fall within a specifically defined area (region) of the brain. In this study, a ROI analysis was conducted in a hypothesis-relevant region (i.e., striatum, rIFG, FEF, SEF) when the region demonstrated a significant response at the whole brain level. The specific boundaries of each ROI were defined by the functional response at the whole brain level (i.e., 6mm sphere centered in the voxel corresponding with the peak *T*-value in each region). In addition to small volume correction analyses conducted in SPM2 for each ROI, the values corresponding with the mean BOLD response was extracted for each ROI and subjected to repeated measures ANOVAs conducted in SPSS 15.0.

The *Incentive (antisaccade vs. prosaccade) vs. No-incentive (antisaccade vs. prosaccade)* contrast yielded a significant group effect in the left striatum, $F(2, 42) = 2.53$, $p<.05$ (Figure 6, 7), and the rIFG, $F(2, 42) = 2.66$, $p<.05$ (Figure 8, 9). *Post hoc* pair-wise comparisons yielded a significantly greater response in left striatum for

adolescence relative to adults ($p<.05$). The adolescent response in rIFG was significantly greater than both adults ($p<.05$) and children ($p<.05$).

The *Incentive (antisaccade vs. prosaccade)* contrast yielded a significant group difference in the right striatum, $F(2, 42) = 2.89$, $p<.05$ (Figure 10,11), and rIFG, $F(2, 42) = 3.15$, $p<.05$ (Figure 12,13). *Post hoc* pair-wise comparisons yielded a significantly greater response in the striatum for adolescents than adults ($p<.05$), and a significantly greater response in rIFG for adolescents relative to both adults ($p<.05$) and children ($p<.05$).

Chapter 5: Discussion

The primary aim of this study was to examine the interaction between reward and inhibitory control processes in childhood, adolescence, and young adulthood. This interaction was assessed via a reward modified antisaccade paradigm administered to children, adolescents and young adults during fMRI scanning. Three key findings emerged. First, adolescents showed greater inhibition-related neural responses than both adults and children when potential monetary incentive was available. Second, adolescents reliably showed greater striatal recruitment with incentive than adults. Adolescent striatal recruitment with incentive was also greater than children, though the difference did not meet statistical significance. These differences in striatal response occurred as all three age groups showed significant behavioral improvements with incentive (relative to with no-incentive). Third, as expected from previous developmental studies (Luna et al., 2001), when incentive was not present, adolescents and children showed deficient inhibitory behavior relative to adults. Findings from this study support models proposing an interaction between heightened adolescent sensitivity to reward and a protracted development of inhibitory control. Additionally, the current findings expand these models by suggesting heightened adolescent sensitivity to reward may be able to facilitate developmentally inefficient inhibitory control processes in a bottom-up manner.

Interaction between reward and inhibitory control processes

Developmental discordance between highly sensitive reward processing systems and immature inhibitory systems are considered a root of the heightened risk-taking, novelty-seeking and exploratory behaviors that characterize adolescence. However,

reward processing and inhibitory control systems are typically studied in isolation, with examinations of their interaction being much less frequent. In the current study, examination of the behavior and neural responses to antisaccades/prosaccades in conditions of incentives/no-incentives allowed the interaction between these two systems to be examined.

Similar to previous behavioral findings (Hardin et al., 2007; Jazbec et al., 2006), children, adolescents, and adults showed better inhibitory behavior with incentive than with no incentive. This reward-related increase in inhibitory control was reflected in greater antisaccade accuracy with incentive than without, and shorter latencies to initiate antisaccades with incentive than without. Additionally, both children and adolescents showed evidence of typical developmental deficits in overall inhibitory behavior (specifically accuracy). This deficit for children and adolescents occurred despite showing a similar magnitude of reward-related improvement as adults.

When correctly inhibiting with incentive, adolescents showed greater striatal recruitment than adults. A similar difference also existed between adolescents and children, though this difference did not meet statistical significance. The lack of statistical significance in the difference between adolescents and children likely resulted from the large amount of variability observed in the child group. Striatal recruitment is associated with reward-related neural coding (Knutson, Adams, Fong, & Hommer, 2001), and converging evidence from multiple areas of study suggests developmental change and heightened arousal in reward-related neural response during adolescence. For example, proliferation and redistribution of dopamine neurons (Chambers, Taylor, & Potenza, 2003; Spear, 2009), and heightened recruitment of the striatum during reward processing

(Ernst et al., 2005; Galvan et al., 2006; van Leijenhorst et al., 2009) are reported during

adolescence. These neural changes likely reflect heightened sensitivity in reward-related

systems, and underlie increased (relative to childhood and adulthood) displays of

sensation-seeking and risk-taking behavior. The greater adolescent striatal response

observed in the current study is consistent with previous developmental studies

examining reward processing (Ernst et al., 2005; Galvan et al., 2006; van Leijenhorst et

al., 2009). Likewise, the current striatal results provide further evidence of a heightened

adolescent reward sensitivity that is reflected at a neural level in a hyper-responsive

striatum in the context of a potential monetary reward.

Age related differences also emerged in the rIFG during inhibition with potential

incentive. The rIFG is implicated in inhibitory control processes (Aron et al., 2004), and

adolescents typically show deficient inhibition-related responses in this region relative to

adults (Bunge, Hazeltine, Scanlon, Rosen, & Gabrieli, 2002; Rubia et al., 2007).

Deficient functional responses in this region parallel reports of deficient inhibitory

behavior during cognitive tasks (Davidson, Amso, Anderson, & Diamond, 2006; Fischer

et al., 1997), and the gradual structural development of the cortex during adolescence

(Lenroot & Giedd, 2006).

In the current study adolescents demonstrated a greater rIFG response relative to

both children and adults. While a greater response relative to children is expected, the

greater adolescent response relative to adults could appear (at first glance) inconsistent

with previous results (Rubia et al.2006). However, the heightened adolescent rIFG

response only occurred with potential incentive, and may represent the modulation of

inhibitory control processes by reward-related processes. While both adults and

adolescents demonstrated enhanced inhibitory performance with incentive, adolescents may have required more inhibitory "effort" to overcome their typical developmental deficit. This "effort" may have been driven by the heightened response of the striatum in anticipation of a potential reward, which in turn facilitated the enhanced rIFG response. This explanation, however, is only speculative, and will need to be followed up by future studies.

Reward and inhibitory processes in adolescent development

As previously discussed, current cognitive neuroscience-based models of adolescent behavior propose a dynamic interaction between reward-related neural systems and inhibitory control-related neural systems. According to these models, reward-related systems show heightened sensitivity to rewards in adolescents relative to children and adults. On the other hand, inhibitory control systems in adolescents follow a slow, linear developmental trajectory and are still immature relative to adults. Thus, the adolescent is left with a highly sensitive reward system that biases the adolescent to seek out reward, coupled with a still immature inhibitory control system that is unable to efficiently exert the top-down control required to thwart the reward seeking bias. Both aspects of this model were observed in the current study. A highly sensitive reward-related system was observed, as adolescents showed a greater reward-related striatal response than adults and (at trend level) children. When reward was not present, a still immature/deficient inhibitory control system was observed in adolescents as they demonstrated less efficient inhibitory behavior than adults. However, it must be noted that the current task specifically examined antisaccade inhibition in the context of

monetary rewards. Further study will be required to generalize to inhibition in other paradigms and in the context of other types of reward.

By examining the interactive nature of reward and inhibitory control processing in adolescents, the current study provides valuable findings that can extend previous models. Previous models have addressed the role of inhibitory processes in exerting top-down inhibitory control over reward-related processes. However, the current findings suggest that the interactive relationship between inhibitory control processes and reward-related processes is bidirectional, and that reward-related processes can have a bottom-up influence on the functioning ability and efficiency of inhibitory control processes. While further studies will be necessary, it is possible that increased reward-related adolescent striatal responses were driving increased inhibitory responses in the rIFG. Additionally, given the greater rIFG response in adolescents than in both children and adults, it is possible the rIFG served a compensatory role that assisted adolescents in overcoming a developmentally typical inhibitory deficit. Thus, it may be beneficial to modify current models that discuss the interactions between reward and inhibitory control processes during adolescence to include how these processes interact in different contexts. In potentially rewarding contexts, it is possible that heightened adolescent reward sensitivity can up-regulate typically deficient inhibitory control processes. While these speculations will require further investigation, the possibility that highly sensitive adolescent reward processes can minimize developmental deficits in cognition points to the possibility of numerous applied applications. For example, the possibility that heightened adolescent reward sensitivity can up-regulate inhibitory control could lead to the development of

novel treatment approaches for common adolescent psychopathologies such as substance abuse and attention deficit hyperactivity disorder.

Future directions

Findings from the current study point to a number of future directions and further study. First, the current findings should be followed-up by analyses examining the connective relationship between striatum and rIFG. Specifically, these connectivity analyses should be conducted in a developmental manner to assess age-related differences in the connective relationship between these two regions. Given evidence that adolescent neural development entails a great deal of change in the fiber pathways between brain regions, future connectivity studies will be highly informative and provide insight into the efficiency changes that are observed during adolescence.

Adolescence is a period of increased emotional liability, as well as an increasing importance of peers and social relationships. For this reason, future studies should also examine the reward-related value and influence to emotionally and socially relevant stimuli. Previous studies (including the current work) rely primarily on monetary incentives as a reward. Future work would that builds from the current study should consider examining the modulation of reward-related processes by primary rewards, rewards with greater ecological relevance to adolescence (i.e. social and emotional rewards), and rewards that are adjusted to individual differences in subjective value.

Future studies should also assess the interactive relationship between reward-related and inhibitory control processes during adolescence as they relate to the development of both individual differences and psychopathology. Adolescence is a

period of increased prevalence for many psychiatric disorders such as anxiety, depression, attention deficit-hyperactivity disorder, and substance abuse. Evidence from both adolescent and adult studies of these disorders implicate a role for both reward and inhibitory processes, and point to dysfunction in reward-related and inhibitory neural pathways. Future research examining adolescent development of the interactive relationship between reward-related and inhibitory control processes may shed light on development of the specific dysfunctions underlying these disorders, and lead to novel treatments and/or preventative measures.

Tables

Table 1. Overview of accuracy and latency findings in developmental antisaccade literature.

Study	Age (years)	Sample size	Task	Accuracy results	Latency Results
Ross et al., 1994	7-15	53	Pro	Pro: No difference with age	Linear decrease w/ age
Fischer et al., 1997	8-70	281	Pro and Anti	Anti: decrease errors until 20; increase after 20	Pro: decrease until 15-20; increase after 30 Anti: steep decrease from 9-15, continued decrease until 25; increase after 25
Munoz et al., 1998	5-79	168	Pro and Anti	Anti: most errors for 5-8	Pro: U-shaped curve, shortest 18-22 Anti: longest for 5-8
Fukushima et al., 2000	4-13 20-38 7-12 20-38	99 22 59 15	Pro Pro Anti Anti	Anti: decrease errors with age	Pro: increase until 12 then plateau Anti: shorter for adults than children
Klein, 2001	6-28	199	Pro and Anti	Anti: decrease errors with age	Pro: decrease with age Anti: decrease with age, decrease to a greater extent than pro
Luna et al., 2001	8-13 14-17 18-30	11 15 10	Pro and Anti	Anti: fewer errors with age	No significant latency differences
Malone & Iacono, 2002	11 17	674 616	Anti	Anti: fewer errors with age	
Luna et al., 2004	8-30	245	Pro and Anti	Anti: decrease errors until 14	Anti: decrease until 15
Klein & Feige, 2005	7-8 10-11 13-14 15-16	12 11 11 12	Pro and Anti	Anti: decrease errors after 10-11	Pro: decrease with age Anti: decrease with age

	17-18	12			
Kramer et al., 2005	8-9	25	Pro and Anti	Anti: fewer errors after 15	Pro: decrease until 13-15
	10-12	25			Anti: decrease until 16-18
	13-15	25			
	16-18	25			
	19-25	25			
Salman et al., 2006	8-19	39	Pro	Pro: No difference with age	Pro: decrease with age
Scherf et al., 2006	10-13	9	Pro and Anti	Anti: fewer errors with age	No significant latency differences
	14-17	13			
	29	8			
Eenshuitra et al., 2007	8-9	19	Pro and Anti	Anti: fewer errors with age	Pro: decrease with age
	11-13	19			Anti: decrease with age
	22	21			

Table 2. Percent of correct saccade responses by incentive and group type. The mean (SD) percent of correct antisaccade and prosaccade responses presented by age group and by incentive condition.

	Prosaccade		Antisaccade	
Group	Incentive	No-Incentive	Incentive	No-incentive
Child	71.9% (3.7)	59.5% (5.9)	55.7% (3.6)	53.6% (3.4)
Adolescent	75.7% (3.7)	66.6% (5.9)	62.8% (3.6)	59.5% (3.4)
Adult	82.4% (3.7)	68.2 %(5.9)	70.6% (3.6)	66.5% (3.4)

Table 3. Latency to initiate correct saccades. The mean (SD) latency to initiate correct antisaccade and prosaccade responses presented by age group and by incentive condition.

Group	Prosaccade		Antisaccade	
	Incentive	No-Incentive	Incentive	No-incentive
Child	289.07 (37.74)	308.96 (42.50)	359.91 (52.43)	365.21 (49.20)
Adolescent	312.03 (37.74)	316.83 (42.50)	339.82 (52.43)	379.1 (42.20)
Adult	335.13 (37.74)	368.14 (42.50)	435.50 (52.43)	445.88 (42.20)

Table 4. Regions showing significant activation during whole brain analysis of the contrast [*Incentive (antisaccade vs. prosaccade) vs. No-incentive (antisaccade vs. prosaccade)*]. This contrast revealed regions that were significantly activated during inhibition in the Incentive condition, while controlling for activation specific to the No-incentive condition. Peak *T*-Value = the largest *T*-value found in each significant region; *k* (cluster) = the size of the significant region of activation; Brodmann Area = the Brodmann area in which the significant region is found; *x, y, z* = the MNI coordinates of the voxel corresponding with the peak *T*-value in each significant region.

Region	Peak *T*-Value	*k* (cluster)	Brodmann Area	*x*	*y*	*z*
Incentive (Antisaccade vs, Prosaccade) vs. No-incentive (Antisaccade vs Prosaccade)						
a) All						
l cerebellum	3.73	152	-	-6	-42	-42
r cerebellum	3.66	177	-	8	-38	-30
inferior temp gyrus	3.48	485	20	42	-4	-36
superior temp gyrus	3.01	560	38	40	8	-12
inferior temp gyrus	2.90	258	37	-50	-70	2
l cerebellum	2.69	428	4	-16	-24	-22
inferior parietal lobe	2.31	147	40	-52	-36	26
uncus	2.24	38	36	-28	-6	-30
b) Adult only						
	-	-	-	-	-	-
c) Adolescent only						
parhippocampal gyrus	2.54	236	19	20	-50	-6
superior temporal gyrus	2.43	38	41	-50	-24	8
l cerebellum	2.40	70	-	-14	-46	-4
inferior frontal gyrus	2.31	121	9	-46	8	32
caudate	2.22	90	-	-6	12	-6
d) Children only						

Region						
r cerebellum	2.99	139	-	16	-32	-16
cingulate gyrus	2.49	1498	31	16	-36	28
cingulate gyrus	2.24	86	24	4	0	24
inferior semi-lunar lobule	2.03	35	-	-26	-72	-44

e) Adolescent vs. Adult

Region						
parhippocampal gyrus	2.94	368	35	-30	-26	-20
posterior cingulate	2.70	452	30	10	-64	10
superior temporal gyrus	2.64	1226	21	52	-6	-12
middle frontal gyrus	2.49	217	9	-46	14	34
superior temporal gyrus	2.46	99	22	-56	-54	6
middle temporal gyrus	2.26	46	22	54	-46	4
caudate head	2.23	40	-	-6	12	-6
claustrum	2.22	41	-	-30	2	12
middle frontal gyrus	2.21	220	6	0	-14	54

f) Adolescent vs. Children

Region						
inferior temp gyrus	3.89	125	20	-40	-2	-40
middle temp gyrus	3.22	164	21	42	-4	-30
substantia nigra	2.98	509	-	6	-8	-14
inferior frontal gyrus	2.95	505	47	48	16	-6
middle frontal gyrus	2.64	125	9	-44	14	32

g) Adult vs. Children

Region						
	-	-	-	-	-	-

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Table 5. Regions showing significant response during whole brain analysis of the contrasts *Incentive (antisaccade vs. prosaccade).* This contrast revealed regions that were significantly activated during inhibition in the Incentive condition. Peak *T*-Value = the largest *T*-value found in each significant region; *k* (cluster) = the size of the significant region of activation; Brodmann Area = the Brodmann area in which the significant region is found; *x, y, z* = the MNI coordinates of the voxel corresponding with the peak *T*-value in each significant region.

Region	Peak *T*-Value	*k* (cluster)	Brodmann Area	*x*	*y*	*z*
Incentive (Antisaccade vs. Prosaccade)						
a) All						
inferior occipital gyrus	4.95	667	18	36	-86	-8
inferior occipital gyrus	4.11	1103	18	-28	-88	-10
parahippocampal gyrus	4.03	219	35	-22	-8	-22
medial frontal gyrus	3.68	214	10	14	34	-8
insula	3.51	707	13	-30	-10	24
superior temporal gyrus	3.09	342	22	-30	-58	14
precuneus	2.96	58	7	-16	-68	36
b) Adult only						
anterior cingulate	3.05	92	35	14	32	-8
hippocampus	2.27	77	-	-28	-44	4
parahippocampal gyrus	2.24	54	35	-22	-10	-22
superior frontal gyrus	2.23	54	6	-12	10	56
superior frontal gyrus	2.20	322	8	-16	20	42
middle temporal gyrus	2.17	247	19	-34	-64	16
putamen	2.00	124	-	-24	-6	22
c) Adolescent only						
inferior occipital gyrus	4.66	254	18	-30	-88	-10

inferior occipital gyrus	4.41	145	18	36	-86	-6
insula	3.24	109	13	30	-8	22
anterior cingulate	3.20	267	32	14	32	-8
caudate head	3.20	67	-	8	16	2
angular gyrus	3.16	190	39	-26	-56	16
caudate body	3.15	614	-	-16	6	18
r cerebellum	3.07	43	-	10	-48	-42
supramarginal gyrus	3.01	38	40	-40	-46	30
cingulate gyrus	2.93	53	31	-16	-46	28
precuneus	2.80	82	4	22	-22	48
caudate	2.79	42	-	20	10	20
insula	2.74	84	13	30	-40	24

d) Children only

superior temporal gyrus	3.96	1271	38	50	10	-18
uncus	3.89	498	28	-26	-8	-28
inferior occipital gyrus	3.08	322	18	36	-86	-8
middle frontal gyrus	2.95	28	6	-18	12	60
l cerebellum	2.94	1655	-	-36	-62	-8
l cerebellum	2.80	363	-	-12	-46	-40
lingual gyrus	2.65	238	18	10	-64	4
insula	2.52	137	13	-38	-2	12
precuneus	2.36	99	31	22	-72	28
parahippocampal gyrus	2.24	250	19	34	-46	2

e) Adolescent vs. Adult

r cerebellum	2.92	456	-	6	-44	-42
lingual gyrus	2.75	165	17	-12	-92	0
l cerebellum	2.51	36	-	-10	-40	-10
occipital gyrus	2.51	124	18	36	-84	-10
caudate tail	2.47	206	-	24	-30	16
caudate head	2.36	145	-	8	14	2
inferior temp gyrus	2.26	80	20	-50	-54	-14
supramarginal gyrus	2.23	172	40	-42	-48	30
subcallosal gyrus	2.20	42	34	22	6	-14
insula	2.13	32	13	30	-10	22

f) Adolescent vs. Children

inferior frontal gyrus	2.98	394	47	20	8	-16
insula	2.69	3105	13	30	-8	22
insula	2.35	359	13	30	-40	22
r cerebellum	2.35	189	-	18	-30	-18
medial dorsal nucleus	2.15	51	-	0	-18	6

g) Adult vs. Children						
superior temp gyrus	2.72	155	38	50	16	-12
l cerebellum	2.66	257	-	2	-42	-40
inferior frontal gyrus	2.34	86	47	32	22	-6
inferior semi-lunar lobule	2.25	95	-	-16	-62	-46
superior temp gyrus	2.00	32	22	54	-6	0

Table 6. Regions showing significant response during whole brain analysis of the contrasts *No-incentive (antisaccade vs. prosaccade).* This contrast revealed regions that were significantly activated during inhibition in the No-incentive condition. Peak *T*-Value = the largest *T*-value found in each significant region; *k* (cluster) = the size of the significant region of activation; Brodmann Area = the Brodmann area in which the significant region is found; *x, y, z* = the MNI coordinates of the voxel corresponding with the peak *T*-value in each significant region.

Region	Peak *T*-Value	*k* (cluster)	Brodmann Area	*x*	*y*	*z*
No-incentive (Antisaccade vs. Prosaccade)						
a) All						
inferior occipital gyrus	4.10	1994	18	34	-86	-8
inferior occipital gyrus	2.82	180	18	-26	-90	-8
left cerebellum	2.79	1416	-	-40	-72	-22
left cerebellum	2.29	137	-	-6	-80	-36
right cerebellum	2.15	66	-	30	-74	-50
b) Adult only						
r cerebellum	3.93	456	-	6	-40	-42
middle temporal gyrus	3.34	2382	21	46	2	-26
pulvinar	3.37	275	-	10	-28	16
Parahippocampal gyrus	2.19	102	36	-32	-26	-22
anterior cingulate	2.18	49	24	8	30	0
paracentral lobule	2.13	58	31	6	-12	46
thalamus	2.12	112	-	-20	-22	4
c) Adolescent only						
-	-	-	-	-	-	-
d) Children only						
subcallosal gyrus	4.24	761	34	12	6	-12
inferior temporal gyrus	4.13	175	20	42	-4	-36
r cerebellum	3.20	89	-	24	-34	-36

e) Adolescent vs. Adult						
-	-	-	-	-	-	-

f) Adolescent vs. Children						
insula	1.97	24	13	34	-34	16

g) Adult vs. Children						
pulvinar	3.07	3052	-	12	-34	12
pulvinar	2.59	62	-	-4	-32	14
middle temporal gyrus	2.39	229	21	52	6	-18
anterior cingulate	2.33	44	24	6	30	-2
precuneus	2.31	678	31	-12	-62	28
postcentral gyrus	2.17	119	2	54	-22	28
l cerebellum	2.17	78	-	-28	-64	-16
precentral gyrus	2.08	112	44	54	10	8

Figures

Figure 1. Developmental trajectories of inhibitory control and reward-related neural systems. Functional development of inhibitory control systems develop with protracted developmental trajectory that continues into adulthood. Reward-related systems show a heightened sensitivity during adolescence relative to both child and adult periods. These two different trajectories result in a functional discordance between inhibitory control and reward-related processes during adolescence, with this discordance manifesting as typical adolescent behaviors.
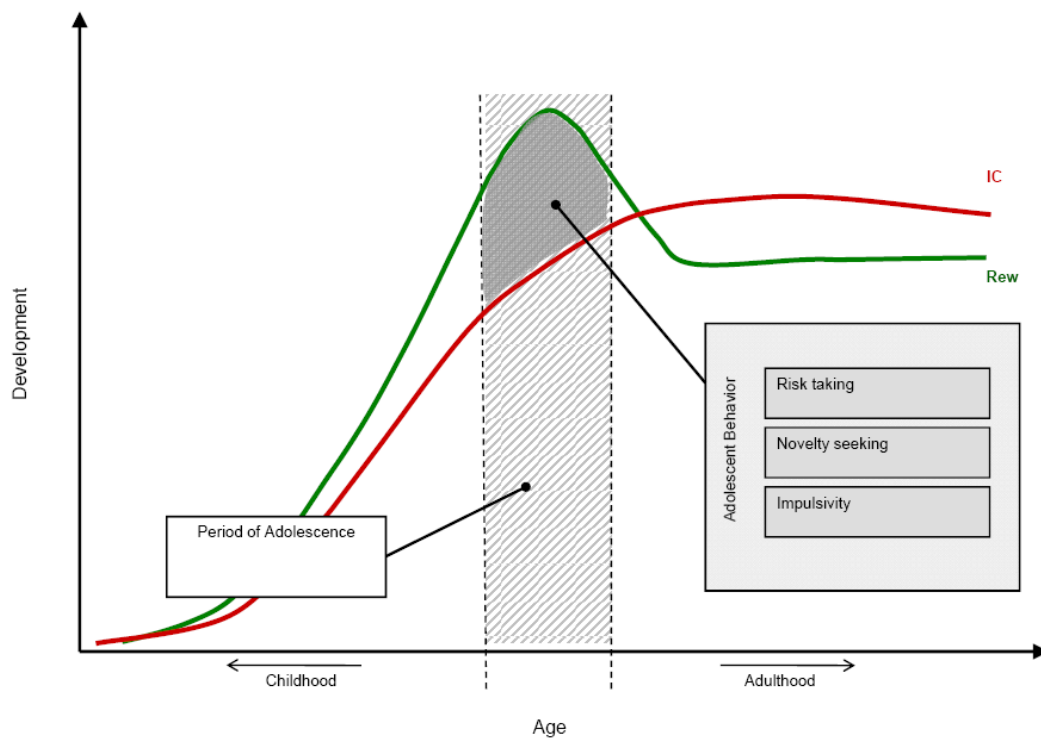
Figure 2. Schematic representation of the typical antisaccade paradigm. The traditional antisaccade paradigm consists of two trials types. During prosaccade trials, the subject is to orient their gaze to a peripherally appearing target. During antisaccade trials, the subject is to inhibit the prepotent response to orient to the peripheral target and instead shift their gaze to the opposite periphery. Deviations of the cue (color in this example) are used to signal the trial type and required saccade type.
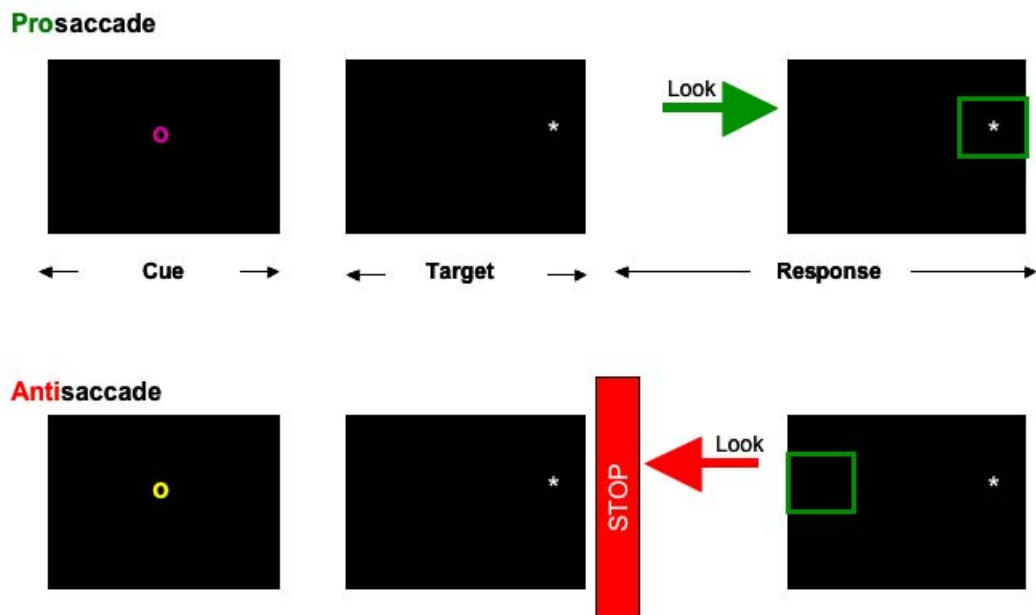
Figure 3. Schematic representation of the Saccade Reward Task. Two different cues were possible. The "$" signaled the potential for incentive, while the "O" signaled no potential for incentive. Each would also appear in one of two possible colors. The color of the cue signaled to make either a prosaccade or antisaccade.
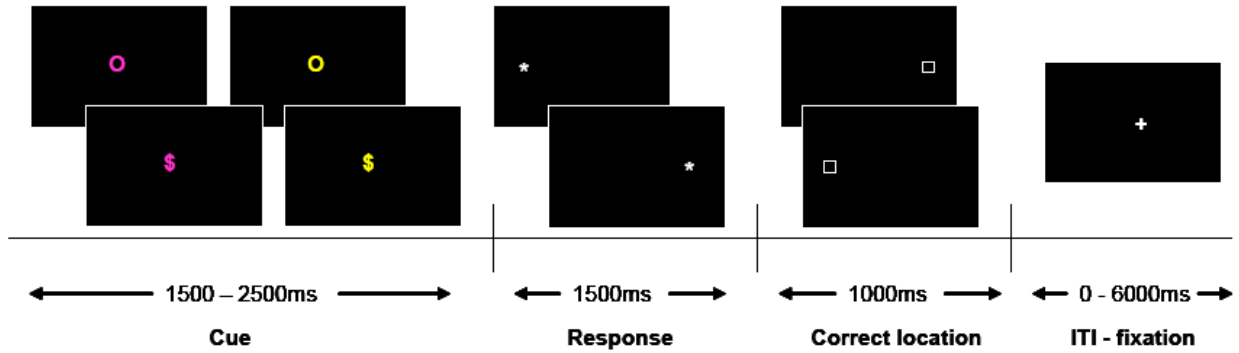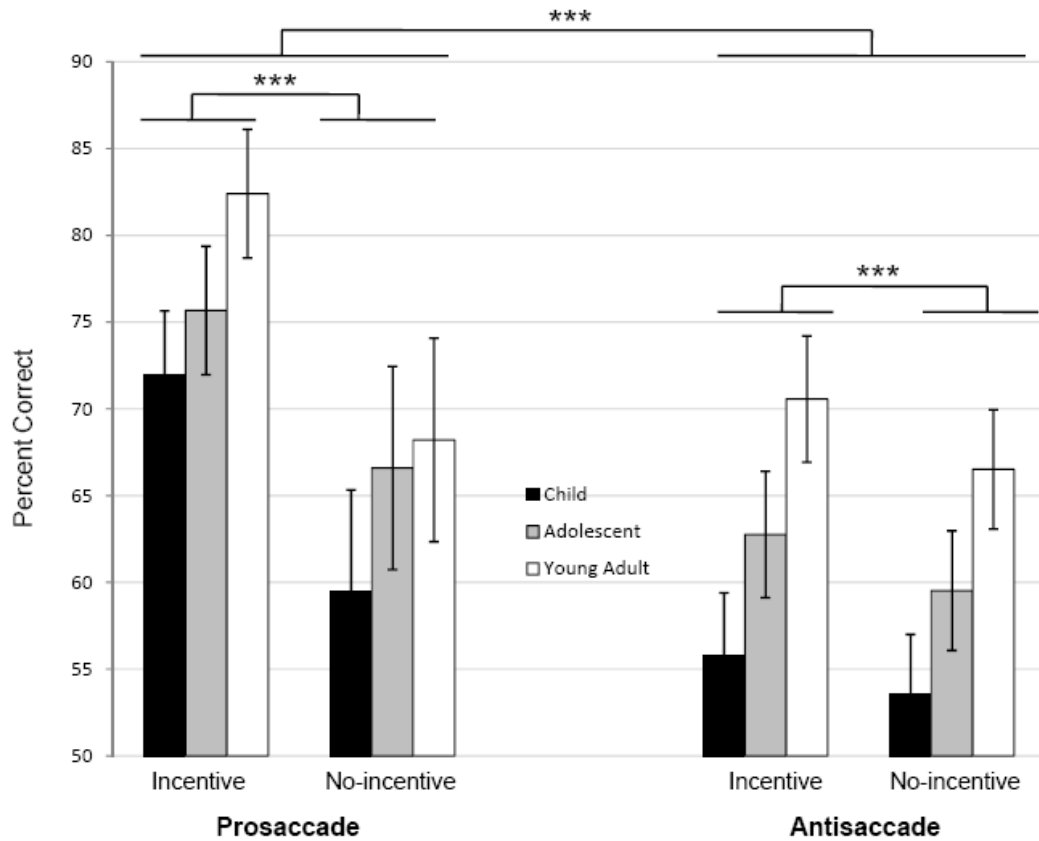
Figure 4. Percent of correct antisaccade and prosaccade responses. An age-group by saccade-type by incentive-type repeated measures ANOVA conducted on the percent of correct responses resulted in: (1) a significant group difference with adults performing better than adolescents, and adolescents better than children; (2) a significant incentive difference as performance was better with potential incentive than with no potential incentive; and (3) a significant saccade difference as performance was better for prosaccades than antisaccades. *** = $p<.001$

Figure 5. Response latency for correct antisaccade and prosaccade responses. An age-group by saccade-type by incentive-type repeated measures ANOVA conducted on the latency in initiate correct responses resulted in: (1) a significant incentive difference as responses were faster with potential incentive than with no potential incentive; and (2) a significant saccade difference as responses were faster for prosaccades than antisaccades. *** = $p<.001$, **=$p<.01$
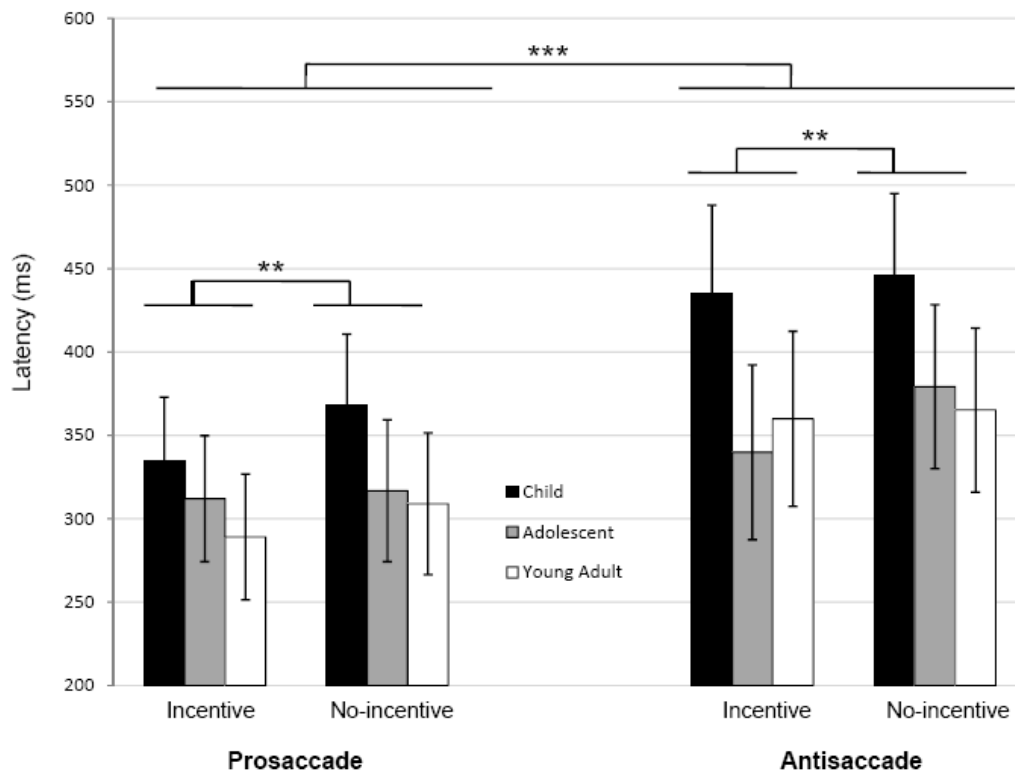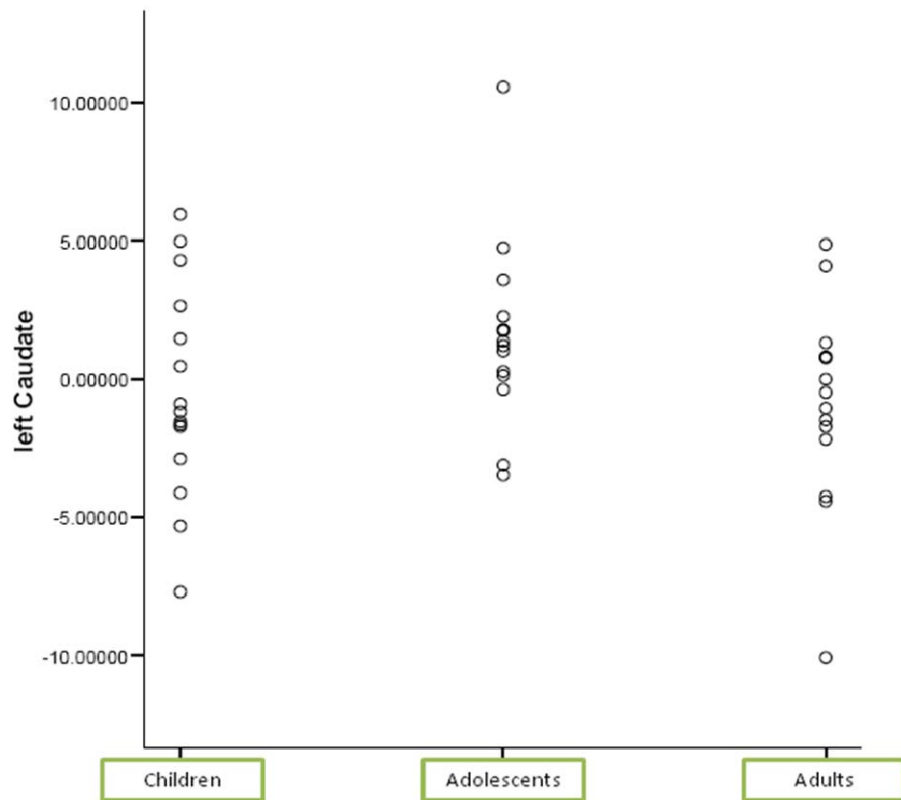
Figure 6. Inhibition-related response during incentive (when controlling for no-incentive) (striatum). The contrast designed to examine the interaction between reward and inhibitory control processes resulted in significant whole brain responses in right caudate (striatum). ROI analyses of the area around the peak (6mm) of the whole brain response revealed a significantly greater striatal response for adolescents relative to young adults. A similar difference also existed between adolescents and children; however this difference did not meet significance.
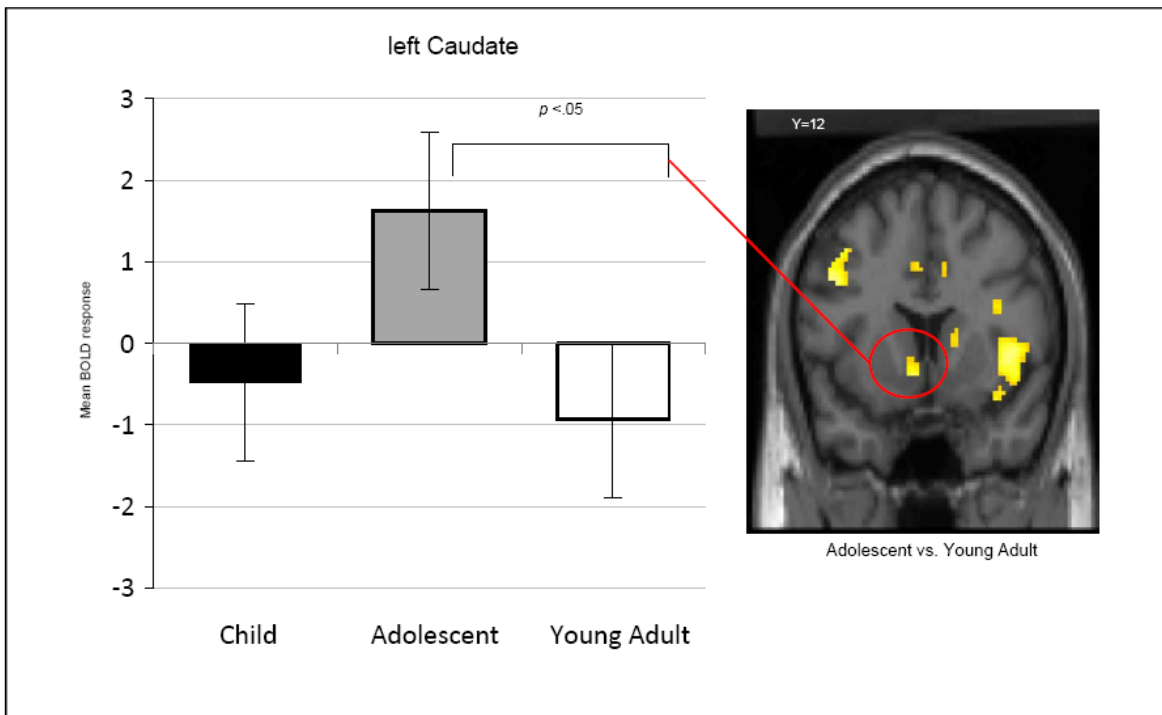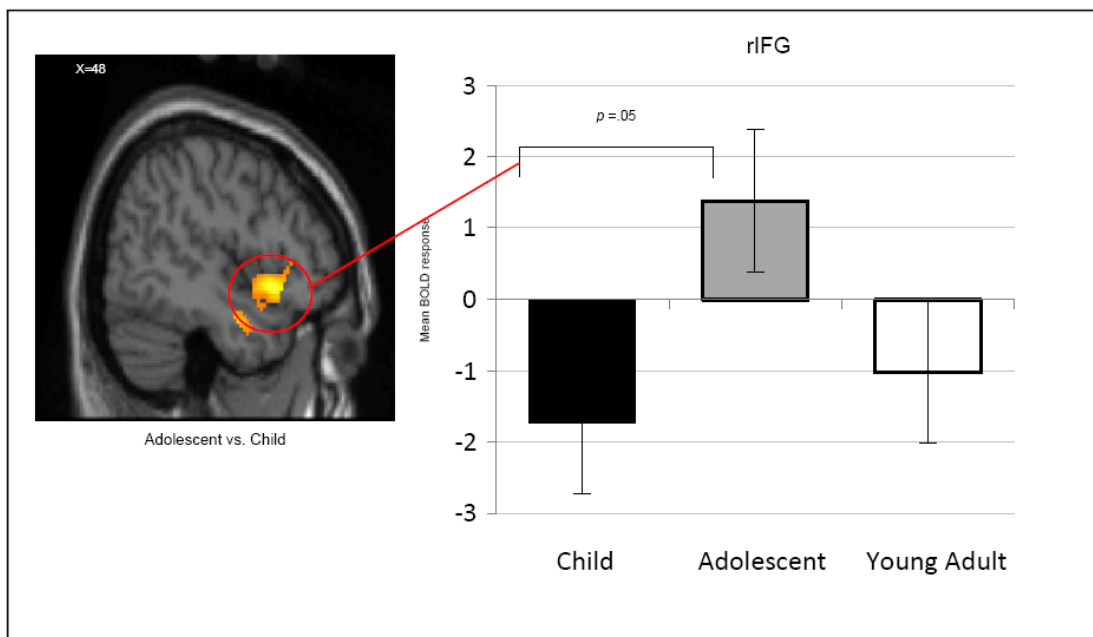
Figure 7. Inhibition-related response during incentive (when controlling for no-incentive) (striatum) – individual participant scatter plot.

Figure 8. Inhibition-related response during incentive (when controlling for no-incentive) (rIFG). The contrast designed to examine the interaction between reward and inhibitory control processes resulted in significant whole brain responses in rIFG. ROI analyses of the area around the peak (6mm) of the whole brain response revealed a significantly greater rIFG response for adolescents relative to children. A similar difference also existed between adolescents and adult, however this difference did not meet significance.

Figure 9. Inhibition-related response during incentive (when controlling for no-incentive) (rIFG) – individual participant scatter plot.
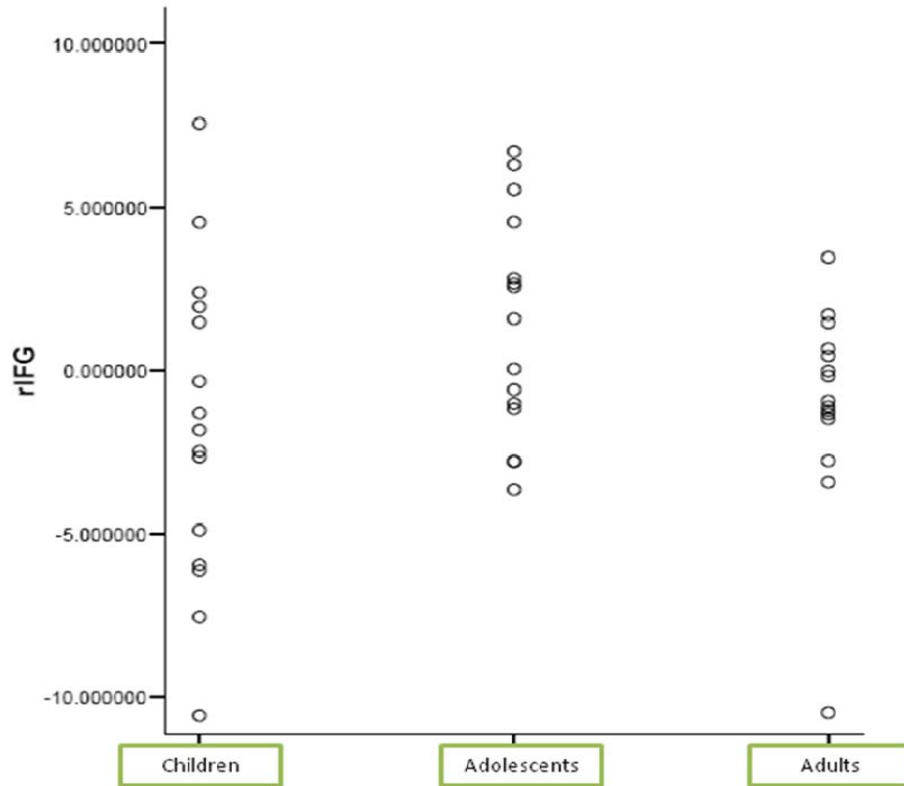
Figure 10. Inhibition-related response during incentive (striatum). A contrast designed to examine the interaction between reward and inhibitory control processes resulted in significant whole brain responses in right caudate (striatum). ROI analyses of the area around the peak (6mm) of the whole brain response revealed a significantly greater striatal response for adolescents relative to young adults. A similar difference also existed between adolescents and children; however this difference did not meet significance.
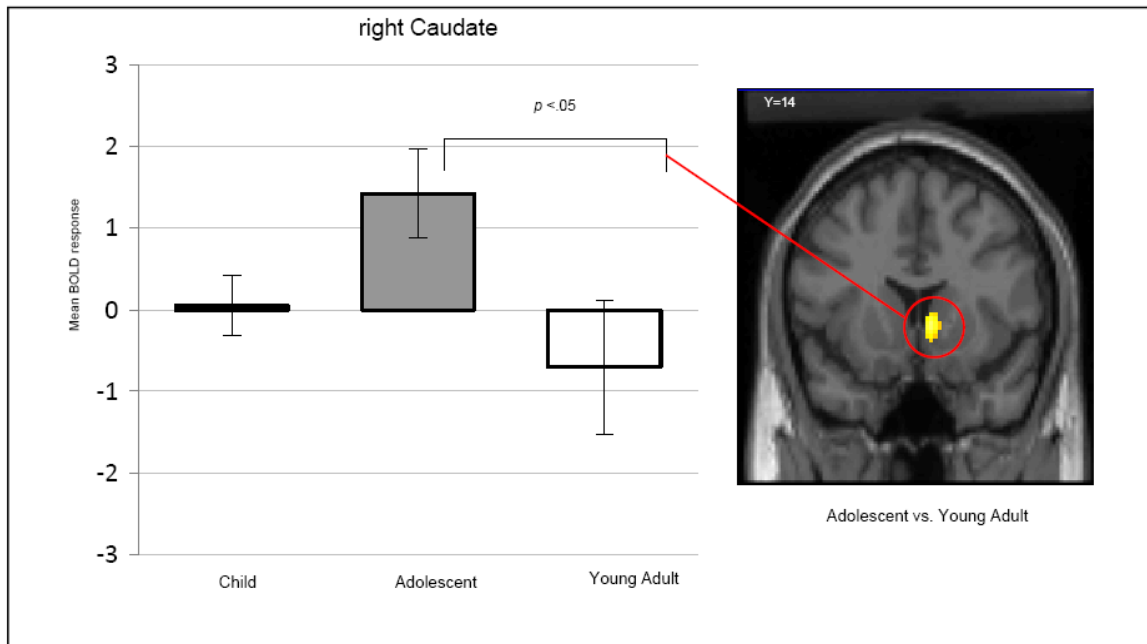
Figure 11. Inhibition-related response during incentive (striatum) – individual participant scatter plot.
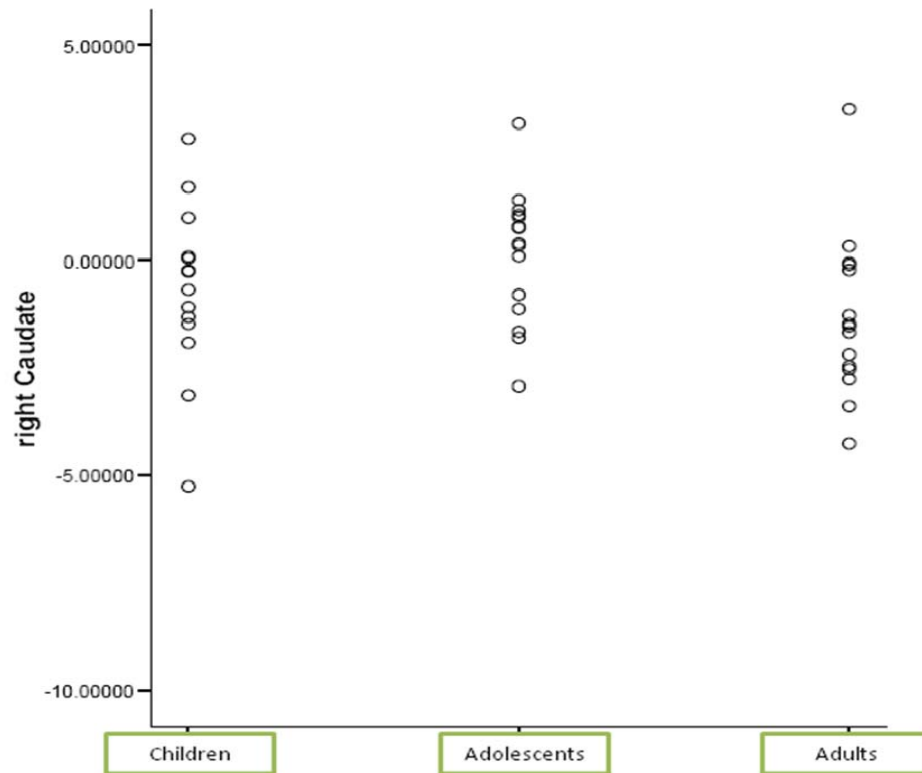
Figure 12. Inhibition-related response during incentive (rIFG). The contrast designed to examine the interaction between reward and inhibitory control processes resulted in significant whole brain responses in rIFG. ROI analyses of the area around the peak (6mm) of the whole brain response revealed a significantly greater rIFG response for adolescents relative to children, and also for adolescents relative to young adults.
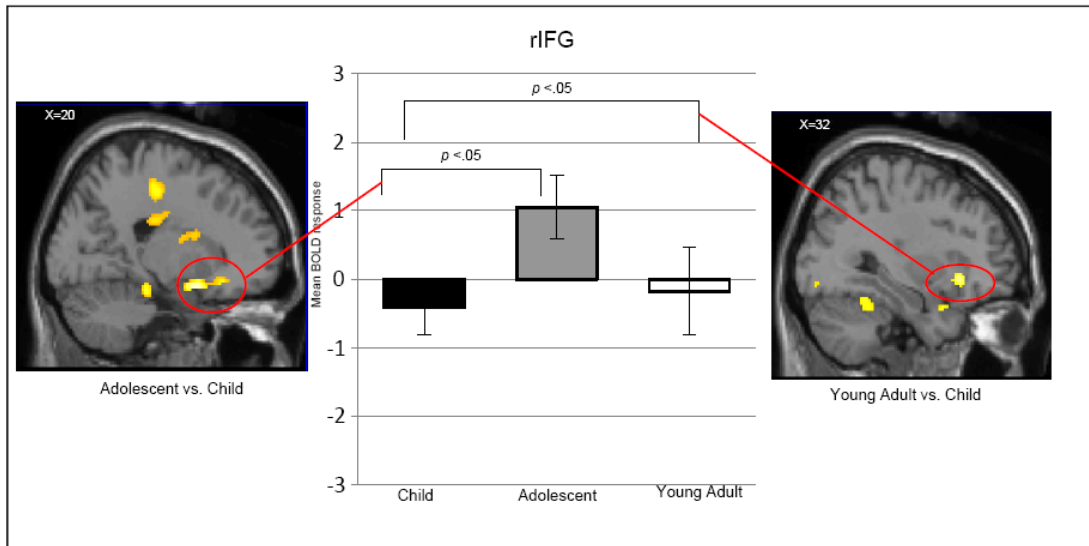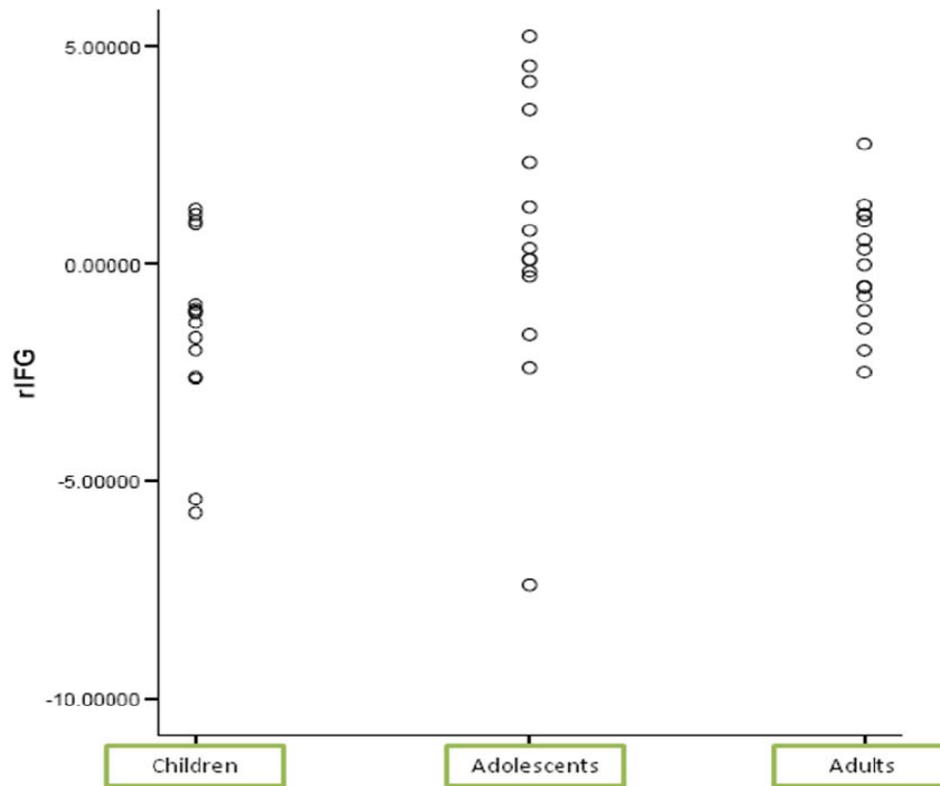
Figure 13. Inhibition-related response during incentive (rIFG) – scatter plot of individual

responses.

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