BIOLOGICAL BASIS OF VARIABILITY IN DOPAMINE AVAILABILITY ON FRONTOSTRIATAL BRAIN FUNCTION IN ADOLESCENCE

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Neurodevelopmental studies indicate a protracted development through adolescence of brain systems underlying incentive-driven behaviors including PFC (PFC) and the striatum. These systems support the executive control of behavior as well as motivationally driven behaviors and may contribute to vulnerabilities in the emergence of psychopathology. The PFC and striatum may support cognition and motivation through the function of the neurotransmitter dopamine. Dopamine (DA) availability is increased during the adolescent period in human and animals and play an important role in mediating individual differences in risk-taking behaviors. This dissertation seeks to examine the moderating role of genetically mediated DA availability on frontostriatal brain function in adolescence. To this end, we genotyped individuals between the ages of 10 and 20 for common functional polymorphisms in three genes that have a direct influence on synaptic DA availability. In addition, we calculated a multilocus composite score in order to assess additive effects of our three genetic loci. We used functional magnetic resonance imaging (fMRI) to assess brain function. The purpose of our first study was to examine the integrity of frontostriatal networks using resting state functional connectivity. We then look more directly at the role of frontostriatal brain function on incentive-driven behaviors using a rewarded inhibitory control task that has a known developmental signature . Overall we found a moderating influence of DA availability on age-related changes in key frontostriatal circuitry suggesting that the maturation of brain function in adolescence may in part be mediated by inter-

individual variability in DA signaling. Overall, the genotypes by age interactions highlight a unique DA-driven brain profile in adolescence. This suggests that a genetically mediated brain phenotype characterized in adolescence may differ significantly from that in adulthood. This has strong implications regarding the variability observed in adolescent risk-taking behaviors as well as predictions of later adult behavior.

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PREFACE

There are a number of individuals to whom I owe a tremendous amount of gratitude for their help and support throughout my graduate career. First, my mentor Dr. Bea Luna, who always encouraged me to pursue my research interests and provided me with thoughtful feedback. She has always been very supportive and positive and granted me latitude to follow my own interests, even when they did not line up with hers. She has given me greater inspiration to pursue lines of research that may be unconventional and advised me to never give up, not matter how challenging it may be to secure funding. She always challenged me to be more confident: “You are not a little girl anymore, you are a scientist”, she often says.

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1.0 INTRODUCTION

In the human lifespan, the adolescent period roughly coincides with the onset of puberty, when key neuroendocrine processes trigger a complex series of biological changes including, significant physical, sexual (adrenarche and gonadarche), neurochemical, neurofunctional, physiological, cardiovascular, and respiratory maturation (Falkner & Tanner, 1986; Romeo, 2003). These biological changes reciprocally interact with the environment to characterize a transitional period, when an individual is transforming into an adult, physically, behaviorally and psychosocially (Spear, 2000). The adolescent period is primarily defined in primates is around age two to four years, in rodents around postnatal day 28 to day 42 or 49, and in humans in the second decade of life with variability due to environmental factors and sex (L. P. Spear, 2000).

Across species, adolescents demonstrate peak levels of sensation/novelty seeking coupled with diminished levels of harm avoidance, leading to an increase in risky behaviors (Laviola, Macri, Morley-Fletcher, & Adriani, 2003). Normative increases in sensation seeking can be adaptive, allowing adolescents to seek independence outside of the home. In other words, *some* risks might be necessary to facilitate the transition into adult roles in society. However, engaging in behaviors with high subjective desirability can also expose an individual to harmful consequences (Spear, 2000). Here we define risk-taking as engaging in a behavior with potential rewarding outcomes, but high potential negative consequences.

Furthermore, evolutionarily adaptive behavior (e.g. leaving the home, finding a mate,

exploring novel environments, and experimentation with novel situations) may not meet the needs of societies in developed nations. Therefore, individuals are often "scaffolded" and supported beyond the teen years into the twenties (Arnett, 2000; Dahl, 2004), as modern society no longer requires adolescents to seek immediate independence, prolongs the education process, and delays mating. Thus, the consequences of risky behaviors seen in adolescence (e.g. experimentation with drugs and alcohol, reckless driving, and unprotected sex) can be dramatic as mortality and morbidity rates demonstrate a significant increase from childhood (Dahl, 2004). From a necessary public health standpoint, the focus of research on adolescence has shifted and lengthened to account for individuals in this "emerging adulthood" stage. In addition to the risks of normative development, adolescence is often a time when various mental illnesses emerge such as mood disorders, drug abuse disorders, eating disorders, and psychoses (Chambers, Taylor, & Potenza, 2003; Paus, Keshavan, & Giedd, 2008; Pine, 2002; Sisk & Zehr, 2005).

Behavioral vulnerabilities during adolescence may arise due to an imbalance between (1) behaviors that are maturing to adult levels (i.e. executive functions, impulsivity and cognitive control of behavior) (Steinberg, 2008) and (2) behaviors that *peak* in adolescence (i.e. sensation and novelty seeking, reliance on peer influences, emotionality) (for review see (Blakemore & Robbins, 2012)) culminating in a *distinct* behavioral profile. Importantly, research demonstrates that adolescence *do* have access to mature decision-making and executive functions (Paus, 2005) and are capable of abstract thinking and rational behavior (Steinberg, Cauffman, Woolard, Graham, & Banich, 2009). However, in the context of highly emotive, reward-seeking states, adolescents often have an increased propensity towards impulsive decision-making, often leading to risky behaviors (Blakemore & Robbins, 2012; Casey, Getz, & Galvan, 2008).

Despite an overall increase in risk taking behaviors in adolescence, there is much

variability in adolescent behavior that remains unexplained. That is, while some adolescents are high risk-takers, others are not, and individual adolescents may at times demonstrate risk-taking behaviors in certain contexts, especially rewarding or emotionally salient ones, and not in others. Despite these individual differences, each individual may be at their own "peak" in sensation seeking during adolescence, highlighting a unique and universal biological vulnerability and neuroplasticity that is not fully characterized.

In the past decade, the field of genetics has merged with cognitive neuroscience providing a non-invasive approach for investigating biologically driven variability in brain function underlying complex behaviors. Using an intermediate phenotype approach, researchers have begun examine the neurobiological basis of variability with the idea that brain function and structure have direct genetic influence. Since then, studies to explore associations between functionally significant genetic variants and brain structure/function have been employed to tease apart the contribution of genetically-driven variation in cellular function to complex behaviors or diseases of interest (Hariri & Weinberger, 2003).

Genes coding for monoamine (e.g. dopamine, serotonin, norepinephrine) neurotransmitter proteins have been of particular interest given their role in modulating brain function underlying behavior. Circuitry that is modulated by dopamine has been widely implicated in a wide range of cognitive functions that mature during adolescence, including working memory, inhibitory control, task switching, and reward processing (Wise, 2004). Abnormalities in dopamine functioning have also been implicated in the pathogenesis of many neuropsychiatric disorders that emerge in adolescence such as substance abuse and schizophrenia, as well as increases in impulsivity, reward seeking, and impaired performance on cognitive tasks (Schultz, 2001; Sedvall, 1990). Importantly, the dopamine system undergoes

significant changes over adolescence, coinciding with heightened risk taking behaviors and the onset of many psychopathologies (Wahlstrom, White, & Luciana, 2010).

The primary objective of this dissertation is to characterize the influence of dopamine as measured by variations in dopamine genes on frontostriatal brain function in adolescence. In this chapter, we first review the literature on the maturation of frontostriatal systems over adolescence, the role of dopamine in frontostriatal circuitry, and in modulating behaviors that are driven by incentives. We then review evidence for the protracted development of the dopamine system over adolescence. We propose a basic model suggesting that the intersection of brain maturation and the development of the dopamine system may result in intra-individual variability in brain function in adolescence that is distinct from adulthood. Lastly, we review common functional polymorphisms in genes that impact dopamine-related processing in frontostriatal circuitry, proposing imaging genetics as a promising methodology by which to examine the role of dopamine in adolescent brain function.

1.1 ADOLESCENT BEHAVIOR: SENSATION-SEEKING AND IMPULSIVITY

The neurocognitive focus of this dissertation is the biological basis of variability in the neural underpinnings of incentive processing and its influence on cognitive control of behavior in adolescence. Incentives are broadly defined here as a motivational cue (appetitive or aversive) that drives a behavior. To this end, motivated behaviors and incentive-driven behaviors will be used interchangeably. Cognitive control is defined as the ability to flexibly engage in goal-directed behavior, while suppressing distractors. Inhibitory control is a component of cognitive control and is defined as the ability to suppress a prepotent/reflexive response in order to

generate a goal-directed behavior. Evidence suggests that adolescents tend to both process incentives differently than adults, are motivated by different things and have difficulty consistently controlling behavior (for review see: (Geier & Luna, 2009), leading to suboptimal and often risky decision-making.

The following sections will describe some of the specific behaviors that underlie adolescent risk-taking, namely sensation/novelty seeking and impulsivity. It is important to note that impulsivity and sensation seeking are qualitatively different traits, and do not necessarily co-occur. This point is further evidenced by studies demonstrating that impulsivity and cognitive control overall appear to mature in a protracted fashion (taking individual differences into account), while sensation seeking follows a more curvilinear pattern, peaking in mid-adolescence (Steinberg et al., 2008).

Adolescents generally demonstrate increased interest in novelty and in acquiring independent status, which leads to seeking out novel situations that they find more rewarding than adults (Adriani, Chiarotti, & Laviola, 1998; Douglas, Varlinskaya, & Spear, 2003). Evolutionarily, novelty and sensation seeking are seen as highly adaptive, allowing the adolescent to explore his/her environment, gain independence, take on adult roles (Kelley, Schochet, & Landry, 2004; L P. Spear, 2010), and seek mates outside their family to avoid genetic inbreeding (L P. Spear, 2010). That is, adolescents often seek out novel experiences that are high in subjective reward value.

Adolescents score higher on scales of sensation seeking than children or adults and demonstrate an overall preference for novelty (Douglas, et al., 2003). Novelty seeking that is undertaken with little regard to potential negative consequences can lead to suboptimal behaviors and indeed adolescents demonstrate an inability to effectively integrate potential risks and are

more likely to engage in behaviors that are risky for a potentially rewarding payout (Rivers, Reyna, & Mills, 2008). This may be due to differences in decision-making abilities as well as basic differences in the experience of reward and punishment. One potential explanation is that adolescents experience a general heightened negative affect thereby increasing the need for highly salient or high incentive stimuli (L. P. Spear, 2000). An alternative theory is that adolescents have a heightened sensitivity to incentive stimuli, especially rewarding stimuli, concurrent with a decreased sensitivity to punishment (Benthin, Slovic, & Severson, 1993; Fishbein et al., 2005). Supporting these theories are studies that have shown that adolescent animals (rodents and non-human primates) seek larger rewards than adults and place higher incentive value on drugs that give a pleasurable feeling (Badanich, Adler, & Kirstein, 2006; Brenhouse & Andersen, 2008; Shram, Funk, Li, & Le, 2006; L. P. Spear & Varlinskaya, 2010; Vastola, Douglas, Varlinskaya, & Spear, 2002). The trajectory of sensation seeking as evidenced by laboratory studies has demonstrated that adolescents have heightened sensation seeking between pre and middle adolescence, following puberty and a decline thereafter into adulthood (Galvan et al., 2006; Stephenson, Hoyle, Palmgreen, & Slater, 2003), with sensation seeking being predictive of self-reported risk-taking and delinquent behaviors (Scott-Parker, Watson, King, & Hyde, 2012).

Immature behaviors in adolescence may be the result not only of a heightened propensity for potentially rewarded outcomes, but the inability to suppress competing sources, and to control impulses. (Casey, Thomas, Davidson, Kunz, & Franzen, 2002; Cauffman & Steinberg, 2000; Eigsti et al., 2006; Luna, Garver, Urban, Lazar, & Sweeney, 2004; Mischel, Shoda, & Rodriguez, 1989). Various studies have suggested that adolescents exhibit increased impulsivity relative to adults, as evidenced by studies of delay discounting, choosing immediate albeit

smaller rewards instead of larger, but delayed rewards (Adriani & Laviola, 2003) and the ability to control impulses continues to develop over adolescence and early adulthood (Galvan, Hare, Voss, Glover, & Casey, 2007) using various impulsiveness scales and laboratory decision-making tasks such as the IOWA Gambling Paradigm (Cauffman et al., 2010; Hooper, Luciana, Conklin, & Yarger, 2004).

One index of impulsivity is cognitive control, or the ability to adaptively and flexibly orient behavior towards a favorable goal while simultaneously suppressing inappropriate actions. Cognitive control of behavior matures in a linear fashion across adolescence. (Bjorklund & Harnishfeger, 1990; Case, 1992; Casey, Tottenham, Liston, & Durston, 2005; Dempster, 1981; Luna, et al., 2004; Luna, Padmanabhan, & O'Hearn, 2010; C. A. Nelson et al., 2000). Several lines of evidence have demonstrated improvements in adolescence on cognitive control tasks such as the Go-No-Go, Flanker, Stroop, Stop Signal and antisaccade (H. S. Levin, Culhane, Hartmann, Evankovich, & Mattson, 1991; Liston, Matalon, Hare, Davidson, & Casey, 2006; Luciana & Nelson, 1998; Luna, et al., 2004; Paus, Babenko, & Radil, 1990; Ridderinkhof, Band, & Logan, 1999; Ridderinkhof & van der Molen, 1997; Scherf, Sweeney, & Luna, 2006; Williams, Ponesse, Schachar, Logan, & Tannock, 1999; Zald & Iacono, 1998). However, although adolescents demonstrate improved cognitive control relative to children, persistent immaturities relative to adults continue to undermine controlled decision-making and these immaturities may bias adolescents towards more impulsive behaviors (Velanova, Wheeler, & Luna, 2008, 2009). Taken together, it has been proposed that a combination of heightened sensation/novelty seeking, sensitivity to incentives, and immature cognitive control of behavior could lead to poor decision-making and ultimately, risk taking (e.g. (Ernst, Pine, & Hardin, 2006; Geier, Terwilliger, Teslovich, Velanova, & Luna, 2010; Steinberg, et al., 2008).

We focus on the intersection of incentive processing and its influence on the cognitive control of behavior and the brain circuitry mediating these processes to begin to characterize a biological model of adolescent behavior. This framework is contingent on the idea that adolescents are biased towards potential rewards (Steinberg, 2004), and immature in cognitive control (Yurgelun-Todd, 2007), with continued maturation in the brain systems that underlie both (Casey, et al., 2008).

1.2 FRONTOSTRIATAL CIRCUITRY

Incentive-driven behaviors are strongly modulated by function in the prefrontal cortex (PFC) and striatum and the dynamic interactions between them. Frontostriatal areas key to motivated behaviors include midbrain (ventral tegmental area and substantia nigra), ventral striatum (including nucleus accumbens), dorsal striatum (including putamen and caudate), and areas of the PFC including the orbitofrontal cortex (OFC), inferior (IFG), middle frontal cortex (MFG), and the anterior cingulate cortex (ACC) (Hikosaka & Watanabe, 2000; Knutson, Westdorp, Kaiser, & Hommer, 2000; Schultz, Tremblay, & Hollerman, 2000). The main neural circuits underlying incentive-driven behaviors, specific to frontostriatal circuitry begin in the midbrain (Ventral Tegmental Area – VTA), which projects to medium spiny neurons in the nucleus accumbens (NAcc) and medial PFC including orbitofrontal cortex (OFC), and anterior cingulate cortex (ACC) (Ikemoto & Panksepp, 1999) via the thalamus. These thalamo-cortico-striatal loops are highly modulated by the neurotransmitter dopamine, which is projected from the VTA and substantia nigra, and are involved in the selection, action, and learning of motivationally

driven behaviors (i.e. reward seeking and/or loss aversion) (Costa, 2007; Graybiel, 2005; Graybiel, Aosaki, Flaherty, & Kimura, 1994; Packard & Knowlton, 2002).

The human striatum is recognized as a core node for incentive processing and resulting behaviors, specifically in the ability to synthesize changing environmental cues and appropriately update behaviors through integration with the PFC by way of overlapping, but functionally segregated pathways (Alexander, DeLong, & Strick, 1986; Di Martino et al., 2008; Postuma & Dagher, 2006). Broadly, these circuits tend to segregate by specific cortical and subcortical regions that are involved and the behavioral function that they underlie. These circuits are the 1) motor and 2) oculomotor that are comprised of a projection primarily from and to motor and somatosensory cortices to the putamen and caudate respectively, 3) higher-order cognition and executive function (lateral MFG to dorsolateral caudate), 4) task switching (lateral OFC to ventromedial caudate), and 5) affective processing (medial OFC and ACC to ventral striatum). Di Martino et al. (2008) demonstrated analogous functionally connected circuits in humans using resting state functional connectivity and functional magnetic resonance imaging (fMRI). Identifying these specific circuitries highlights the importance of frontostriatal networks in distinct but overlapping aspects of behavior, specifically ones that are driven by incentives.

The striatum is composed of the dorsal striatum, which includes the caudate and putamen nuclei and the ventral striatum including the nucleus accumbens (NAcc). The striatum has connections with the globus pallidus, substantia nigra, ventral tegmental area and subthalamic nucleus, together constituting the basal ganglia. The most abundant neurons in the striatum are medium spiny neurons, which are GABAergic (Graveland & DiFiglia, 1985) and allow for inputs from various areas of the cortex and subcortical regions. These neurons are also strongly connected with brain stem motor areas, rendering a strong influence of striatum over motor

output. Efferents from midbrain neurons to striatum also serve to modulate cortico-striatal signaling (Nisenbaum, Grace, & Berger, 1992). The ventral striatum (specifically NAcc) acts as a gateway region for converging projections from other limbic structures (amygdala, hippocampus, thalamus) and PFC. The ventral striatum is recognized as a primary region supporting incentive processing (both appetitive and aversive), through its interconnectivity with medial PFC, amygdala, hippocampus, enterhinal cortex, ventral tegmental area and substantia nigra (Chikama, McFarland, Amaral, & Haber, 1997; Di Martino, et al., 2008; Fudge, Kinishio, Walsh, Richard, & Haber, 2002; Haber, Kunishio, Mizobuchi, & Lynd-Balta, 1995; Schoenbaum & Setlow, 2003; Selemon & Goldman-Rakic, 1985). Through interconnectivity with the ventral region, the dorsal striatum also contributes to reward processing, influencing motor control and reward-modulated learning (Delgado, Locke, Stenger, & Fiez, 2003; Leon & Shadlen, 1999). Lastly, the striatum has strong connections to the PFC and the dynamic interactions between the striatum and PFC are critical for motivated behaviors.

The PFC, which is divided into specialized regions, is involved in the integration of information from various brain regions supporting the processing of sensory stimuli, memory, and motor execution and is highly involved in decision making, working memory, cognitive control, and various goal-directed behaviors. (Fuster, 1989; Rushworth, Noonan, Boorman, Walton, & Behrens, 2011). Excitatory glutamatergic pyramidal neurons are the primary efferents from PFC to striatum, and are strongly regulated by each other as well as local inhibitory GABAergic interneurons (O'Donnell, 2010).

In addition, the PFC and dopaminergic midbrain are reciprocally interconnected, with output from the PFC neurons exerting inhibitory control (through GABAergic mechanisms, leading to a disinhibition of striatal neurons) over subcortical dopaminergic regions, which, in

turn, provide efferents to PFC (Carlsson et al., 2001). Segregated pathways between striatum and PFC are vital to a number of behaviors including, learning, motivation, affective responses, action selection, hedonic value expectations, association learning, and executive functions (Alexander, et al., 1986; Di Martino, et al., 2008).

1.3 FRONTOSTRIATAL CIRCUITRY IN ADOLESCENCE

1.3.1 Structural Development

The brain undergoes extensive reorganization over adolescence. First, a number of micro-changes influence neuronal activity in frontostriatal circuitry over adolescence including an overexpression of receptors for serotonin, dopamine, adenergic, and endocannabinoids (Lidow & Rakic, 1992), a peak in the density of interneurons (Anderson, Classey, Conde, Lund, & Lewis, 1995; Erickson & Lewis, 2002; Lewis, 1997), an increase in levels of GABA (Hedner, Iversen, & Lundborg, 1984), and a change in the expression of glutamate activating NMDA receptors on interneurons in the PFC. These changes alter the excitatory-inhibitory balance in neuronal signaling that refine controlled processing into adulthood.

In addition there are large-scale structural and functional changes in the brain over adolescence, due to a combination of increased myelination in cortical to subcortical axons, changes in axon caliber, pruning of synapses and receptors, cell shrinkage, and glial changes (Andersen, 2003; Benes, Turtle, Khan, & Farol, 1994; Rakic, Bourgeois, Eckenhoff, Zecevic, & Goldman-Rakic, 1986; Yakovlev & Lecours, 1967), which refine the developing brain and

strengthen and consolidate highly used connections, while weakening or eliminating redundant or weakly used connections through unique experiences (Giedd et al., 1999; Huttenlocher, 1990; Jernigan, Trauner, Hesselink, & Tallal, 1991; Pfefferbaum et al., 1994). The PFC (both medial and middle frontal gyri) shows continued pruning (Andersen, Thompson, Rutstein, Hostetter, & Teicher, 2000; Huttenlocher, 1979, 1990; Huttenlocher & Dabholkar, 1997) and gray matter thinning through adolescence into early adulthood (Giedd, et al., 1999; Gogtay et al., 2004; Sowell et al., 1999; Toga, Thompson, & Sowell, 2006). Lateral PFC and temporal cortex (also known as higher-order association areas) mature the latest and often show development into the third and fourth decade of life (Gogtay, et al., 2004; Sowell, Thompson, Holmes, Jernigan, & Toga, 1999; Sowell, Thompson, Tessner, & Toga, 2001; Sowell, Trauner, Gamst, & Jernigan, 2002), relative to areas that are stable in childhood such as visual cortex. Although there is evidence for striatal maturation as well over adolescence, findings are mixed and it appears to be in more *dorsal* areas rather than ventral, which are important for cognitive functions (Sowell, Thompson, Holmes, Batth, et al., 1999).

Furthermore, the structural *connectivity* between frontal and striatal regions continues to mature over adolescence. Animal studies indicate continued myelination through adolescence in cortical-subcortical axons (Benes, et al., 1994). Similarly in humans, Diffusion Tensor Imaging (DTI) studies that measure white matter integrity show a protracted maturation of frontostriatal connections through adolescence (Asato, Terwilliger, Woo, & Luna, 2010). White matter development may occur at different rates in different areas of the brain, with subcortical to cortical projections developing at slower rates relative to other tracts (Lebel, Walker, Leemans, Phillips, & Beaulieu, 2008; Peters et al., 2012).

These changes in brain structure have also been found to be associated with improvements in executive function. For example, Liston et al. (2006) found that increased white matter integrity indices in DTI of frontostriatal tracts were correlated with improved performance on a cognitive control over adolescence. Other studies have demonstrated similar trajectories of white matter strength and pruning over tasks assessing working memory (Nagy, Westerberg, & Klingberg, 2004; Olesen, Nagy, Westerberg, & Klingberg, 2003), and delay discounting (Olson et al., 2009).

1.3.2 Functional Development

Concurrent with structural changes are changes in brain activity as measured by functional neuroimaging. For example, studies using positron emission tomography (PET) have shown that glucose metabolism increases from birth to adolescence with a subsequent decline into adulthood in both humans and non-human primates (Chugani, Phelps, & Mazziotta, 1987; Jacobs et al., 1995). These changes in glucose metabolism are thought to be reflective of an increase in synaptic density and neurotransmitter availability followed by a subsequent decline over adolescence.

Functional neuroimaging (specifically fMRI) studies suggest that adolescents demonstrate differential ventral striatal and PFC activity relative to adults when processing incentives (Bjork et al., 2004; Bjork, Smith, Chen, & Hommer, 2010; Ernst et al., 2005; Galvan, et al., 2006; Padmanabhan, 2011; van Leijenhorst et al., 2010). Key differences in incentive-related signaling in adolescence may influence motivationally-driven behaviors and differences in reward reactivity in ventral striatum may be one mechanism that underlies impulsive, reward-mediated decisions, with evidence suggesting that adolescents can alter cognitive performance

when presented with a reward incentive (Geier, et al., 2010; Padmanabhan, 2011). Indeed, increased ventral striatal signaling in adolescence has also been positively correlated with self-reported risk-taking (van Leijenhorst, et al., 2010), increased errors in suppression of an approach response (Somerville, Hare, & Casey, 2010), sensation seeking scores, and externalizing behaviors (Bjork, et al., 2004; Bjork, et al., 2010). As the ventral striatum is highly involved in motivational salience, assessment of appetitive cues and a bias towards rewarded behaviors, dysregulation of the striatum may contribute to impulsive decision-making (Kable & Glimcher, 2007; McClure, York, & Montague, 2004; Robbins & Everitt, 1996). The OFC is involved in the more executive assessment of incentive processing (especially reward processing), in response selection that is associated with incentive-based learning, and has consistently shown reduced reward related activity in adolescence (Frank & Claus, 2006; Galvan, et al., 2006; Geier, et al., 2010; Padmanabhan, 2011; van Leijenhorst, et al., 2010; Van Leijenhorst et al., 2009). Lastly, the dorsal anterior cingulate cortex (dACC), has shown decreased error monitoring related processing in adolescence relative to adults (Velanova, et al., 2008), providing evidence for immaturities in the ability to monitor and flexibly alter behaviors when necessary.

Motivationally-driven behaviors are supported by a widely distributed circuitry of which connectivity between brain areas plays an crucial role (Jahfari et al., 2011). Functional connectivity between cortical-subcortical regions is strengthened over adolescence supporting improvements in tasks of cognitive control (Hwang, Velanova, & Luna, 2010; Stevens, Kiehl, Pearlson, & Calhoun, 2007). For example, a study of effective connectivity during an inhibitory control fMRI paradigm indicated that top-down modulation from prefrontal to striatal regions strengthen between childhood and adolescence and prefrontal to thalamic connections strengthen

between adolescence to adulthood (Hwang & Luna, 2011; Hwang, et al., 2010), highlighting the protracted development of key connections throughout adolescence. Similar findings are reflected in resting state connectivity where core brain networks are generally established by adolescence with subsequent specialization of connectivity into adulthood (Hwang, Hallquist, & Luna, 2012).

Recent neurobiological models of adolescent development suggest that an over active adolescent motivational system (heightened sensation seeking) with a still maturing cognitive system may create a functional imbalance in optimal behavioral regulation (i.e. suppressing a potentially rewarding, but inappropriate behavior) thereby enhancing risk taking behavior in adolescence. The "triadic model" proposed by Ernst et al. (2006) suggests that during adolescence there is an imbalance between enhanced responsivity of positive stimuli (approach behaviors) supported by the striatum, decreased responsivity to negative stimuli (avoidant behaviors) supported by amygdala, in the context of immature prefrontal control of choice selection, resulting in a predisposition to engage in reward driven behaviors. Similarly, another model proposed by (Casey, et al., 2008), suggests that a frontostriatal imbalance may be due to a primacy in the maturation of motivational over executive systems (earlier maturation of subcortical regions, namely striatal, compared to continued limitations in prefrontal function) (Casey, et al., 2008). The social information processing model introduced by Nelson et al., (2005) suggests that functionally distinct networks (or nodes) that serve to determine which stimuli are socially relevant (detection node), emotionally salient (affective node), and plan and execute goal directed behaviors accordingly (cognitive-regulatory node), are refined and changed over adolescence. These changes may exacerbate emotional experiences in social situations and lead to aberrant decision making as a result. Taken together, these models highlight that the

integration of and coordination between executive and limbic regions contribute to a distinct adolescent brain (and subsequently behavioral) phenotype, and that the changes observed in risk taking may be due to dynamic maturation in the connectivity between these areas during adolescence (Sturman & Moghaddam, 2011).

Taken together these studies suggest that protracted structural maturation of the brain may underlie age related differences in cognitive control and response to incentives. By identifying the mechanisms that drive these large-scale functional changes, we can begin to understand not only the underlying basis of variability in behavior, but time points at which the brain may be especially vulnerable to disturbances that lead to the emergence of psychiatric illness. In addition to maturation in systems-level brain function and structure, there are also known age related changes at a finer scale, in cellular-level brain processes such as in neurotransmitter function.

1.4 DOPAMINE

Specialized brain areas subserving affective, cognitive and motor processing are significantly modulated by the neurotransmitter dopamine (DA) (for reviews see (Cools, 2008; Schultz, 2002; Wise, 2004). DA, which primarily modulates fast-acting synapses (glutamate and GABA), extensively innervates striatum and PFC, and modulates a strong reciprocal relationship between both structures (Cools, 2008). Cortico-striatal loops (via the thalamus) are strongly modulated by DA afferents from the ventral tegmental area (VTA) and substantia nigra, which are strongly associated with motivated behaviors including activation of specific reward-seeking behaviors, learning, coding of reinforcements to a specific behavior, motor planning and execution, error

monitoring, and coding valence, salience and expected value of stimuli (Costa, 2007; Graybiel, 2005; Graybiel, et al., 1994; Packard & Knowlton, 2002). DA is synthesized in the midbrain and is utilized throughout the brain, and significantly in striatum and PFC. DA neurons in the midbrain project to medium spiny neurons in the NAcc as well as pyramidal neurons in the PFC and thereby modulate the firing rates of these neurons (Grace, Floresco, Goto, & Lodge, 2007). To this end, DA is significant in modulating function in frontostriatal pathways that subserve cognitive, motivational, and affective processing. Importantly, research demonstrates an inverse relationship between midbrain DA release into striatum and DA neurotransmission in PFC, with output from the PFC neurons exerting inhibitory control over subcortical DA neurons which, in turn, provide afferents to PFC (Jackson, Frost, & Moghaddam, 2001; Meyer-Lindenberg, Kohn, Kolachana, Kippenhan, Inerney-Leo, et al., 2005; Pycock, Kerwin, & Carter, 1980), which can serve to inhibit competing stimuli when engaging in a goal-directed behavior.

Two main types of DA receptors (D_1-like or D_1 and D_5 and D_2-like or D_2, D_3, D_4) are found on dendrites of post-synaptic cells. D_1 receptors when activated by DA, enhance NMDA currents by stimulating adenylyl cyclase activity, thereby increasing cyclic adenosine monophospate, resulting in an excitatory effect within the cell (Kebabian & Calne, 1979; Seamans, Durstewitz, Christie, Stevens, & Sejnowski, 2001). Conversely, D_2 receptor activation results in an inhibitory or no effect on cyclic adenosine monophospate, attenuating NMDA responses resulting in a relative reduction or no change in cell firing (Gulledge & Jaffe, 1998; Tseng & O'Donnell, 2004). Both subtypes of DA receptors are found throughout striatum and PFC, although relative densities of receptor sub-types differ. Specifically in striatum, D_1 receptors are abundant in the direct pathway, thereby exciting neurons that project to the internal segment of the globus pallidus (GPi), increasing inhibition of the GPi, which consequently

disinhibits the thalamus. D_2 receptors, which are abundant in the indirect pathway, decrease firing rates of neurons that project to the external segment of the globus pallidus (GPe), increasing the excitation of GPe neurons that inhibit the subthalamic nucleus (STN) which consequently inhibits the GPi, resulting in an overall inhibition of the thalamus (Gerfen et al., 1990). In this manner, DA serves to modulate behaviors that have higher value and that are reinforced with positive outcomes and inhibit behaviors that have a lower value.

DA neurons are thought to be excited in the anticipation of rewards and inhibited in anticipation of a decrease in reward value (Schultz, 2001). In the PFC, there are more D_1 receptors than D_2, suggesting that DA modulation in the PFC primarily has an excitatory influence (Farde, Halldin, Stone-Elander, & Sedvall, 1987; Goldman-Rakic, 1990; Lidow, Goldman-Rakic, & Rakic, 1991). Furthermore, D_2 receptors are more abundant in the striatum than in the PFC (Camps, Cortes, Gueye, Probst, & Palacios, 1989). Proteins that regulate DA transmission include DA transporters and autoreceptors, which are involved in DA reuptake, and enzymes such as monoamine oxidase (*MAOA* and MAOB) and cathechol-o-methyltransferase (*COMT*), which work to remove DA from the extra-synaptic space. The function of these proteins strongly influences the functional and temporal dynamics of DA transmission. In the PFC, where DA transporters and DA autoreceptors are relatively scarce, DA is primarily degraded by *COMT* and *MAOA* (Bannon, Wolf, & Roth, 1983; Meador-Woodruff, Damask, & Watson, 1994)

DA levels are modulated by two dissociable processes of DA discharge, (1) a constant background tonicity regulated by baseline firing of DA neurons which fires in the 2-10 Hz frequency and (2) a burst firing high-amplitude phasic release (15-30 Hz) (Bilder, Volavka, Lachman, & Grace, 2004). Processing of environmentally salient stimuli results in phasic DA

release on the postsynaptic terminals of DA neurons and tonic DA levels regulate the amplitude of phasic response (Goto, Otani, & Grace, 2007), although research also suggests that phasic DA potentiates tonic DA (Niv, Daw, Joel, & Dayan, 2007). These two mechanisms of DA signaling have been found to lead to distinct behaviors (Floresco, West, Ash, Moore, & Grace, 2003). Fast phasic events occur in response to salient events. For example, DA cells fire in bursts when presented with unexpected reward, novelty, or when making predictions of reward, which serve as important learning signals for error detection and modulate behavioral changes in response to the environment (Schultz, 1998). Slow changes in tonic levels of DA allow for an organism to respond to environmental cues associated with reward, as reinforcement, in response to aversive stimuli (Schultz, 1998), and regulate phasic signaling (Bilder, et al., 2004). As such, the tonic signal may be transcribed into a "trait" related process (i.e. an individual's baseline propensity towards certain types of reward) whereas transient phasic signaling may establish a context-dependent "state" (an instantaneous reaction to a salient event), which in turn (and over time) can modulate further tonic firing. The complex and reciprocal interplay of phasic and tonic DA signaling is necessary for goal-directed behaviors, processing and integrating reward-related information, as well as learning and memory (Floresco, et al., 2003).

The impact of DA on neuronal functioning has been found to have an inverted U shape dose-response curve where extreme DA activity in the PFC results in maladaptive cognitive and behavioral abilities and mid-levels in relatively improved signaling e.g. (Vijayraghavan, Wang, Birnbaum, Williams, & Arnsten, 2007). A hypo or hyper- dopaminergic state, which disrupts the balance of D_1/D_2 receptor binding, decreases the signal-to-noise ratio of neuronal firing, consequently worsening cognitive performance and efficiency of neural circuit function (Weinberger et al., 2001). Individuals with low levels of tonic prefrontal DA (as measured by

genotype), typically perform worse on working memory tasks, but demonstrate improvements with pharmacologically induced increases in prefrontal DA (Cools & D'Esposito, 2011), whereas pharmacologically, increasing prefrontal DA does not provide an added benefit in cognitive performance to individuals with relatively high baseline levels of DA (Kimberg, D'Esposito, & Farah, 1997; Mattay et al., 2000). Similarly, individuals with higher levels of striatal DA availability (as measured by DA transporter activity with genotype) demonstrated decreased activity in striatum and PFC during a memory task compared to individuals with intermediate levels (Bertolino et al., 2009).

The DA system is also posited to influence individual variability in sensation-seeking and impulsivity (Zuckerman, Ballenger, & Post, 1984), with the increased availability for the D_2 receptor in the NAcc being negatively associated with impulsivity (Dalley et al., 2007) and novelty seeking (Zald et al., 2008). Individuals with low DA synthesis in striatum were found to have low working memory capacity in a positron emission tomography (PET) study (Cools, Gibbs, Miyakawa, Jagust, & D'Esposito, 2008). Studies have also shown that individuals with increased levels of DA in striatum may be more impulsive (Dalley, et al., 2007; Forbes et al., 2009), have a propensity to engage in appetitive behaviors, demonstrate improvements in incentive related learning (Frank, 2005; Schultz, 1997), and demonstrate increased neural responses to rewarded stimuli relative to individuals with less striatal DA availability (Dreher, Kohn, Kolachana, Weinberger, & Berman, 2009; Forbes, et al., 2009). Furthermore, impulsive traits have been found to mediate individual differences in response to DA agonists in PFC and influence cognitive performance (Cools, Sheridan, Jacobs, & D'Esposito, 2007). In sum, individual variability in behavior and cognitive abilities may be highly influenced by differences in baseline DA signaling, and pharmacological manipulations may be highly dependent on

baseline state. Lastly, DA signaling and it's influence on neuronal processes undergoes change over adolescence, which can have strong implications for variability in behavior that may differ in adolescence relative to adulthood.

1.5 DOPAMINE IN ADOLESCENCE

The literature spanning the development of DA function and implications for adolescence behavior has been reviewed in depth elsewhere, (Chambers, et al., 2003; Luciana, Wahlstrom, Porter, & Collins, 2012; O'Donnell, 2010; L. P. Spear, 2000; Wahlstrom, Collins, White, & Luciana, 2010; Wahlstrom, White, et al., 2010). Much of the evidence on DA functioning in adolescence is from animal research, notably non-human primates and rodents and the evidence is not straightforward, making for adolescent behavior challenging. With this caveat in mind, the relevant literature is briefly summarized below to highlight an overall trend that may have implications for adolescent behavior.

A peak in activity of midbrain DA neurons has been documented in the rat model (McCutcheon, White, & Marinelli, 2009), suggesting an overall increase in DA levels. Other studies have that basal DA concentrations peak in *late* adolescence with a subsequent decline in adulthood ((Badanich, et al., 2006; Philpot, Wecker, & Kirstein, 2009). Non-human primate studies have suggested the highest concentrations of DA are in the PFC in adolescence and increase before dropping down in adulthood (Goldman-Rakic & Brown, 1982). In human studies, DA levels in the striatum increase until adolescence and then decrease or remain the same (Haycock et al., 2003). In one study, extracellular levels of DA in the NAcc have been

found to be lower in adolescence compared to adulthood (Cao, Lotfipour, Loughlin, & Leslie, 2007).

Dopaminergic innervation to the PFC increases over adolescence (Benes, Taylor, & Cunningham, 2000; Rosenberg & Lewis, 1995), with the largest increase being in cortical layer III, a region that that is highly implicated in cognitive processing. These changes occur both in length of individual axons and as well as total number of projecting axons (Lambe, Krimer, & Goldman-Rakic, 2000; Rosenberg & Lewis, 1994). There is also an increase in the density of synapses between DA neurons and pyramidal neurons in layer III of cortex (Lambe, et al., 2000) and a peak in glutamatergic connectivity from the PFC to the NAcc, specifically in D_1-expressing neurons (Brenhouse, Sonntag, & Andersen, 2008).

Furthermore, non-human primate evidence suggests that D_1 and D_2 receptor densities in PFC increase at different rates, with D_1 receptor density demonstrating earlier peaks (early adolescence) than D_2, which peak in late-adolescence/early adulthood (Tseng & O'Donnell, 2007). Post mortem human studies have also demonstrated that D_1 receptor densities peak around 14-18 years of age (Weickert et al., 2007). Studies have also found that an increase in cells containing D_1 receptors in the PFC from childhood to adolescence and decline from adolescence into adulthood (Andersen, et al., 2000; Weickert, et al., 2007).

In contrast to the PFC, in the striatum, peaks in both D_1 and D_2 receptors occur in childhood and begin to decline in adolescence, evident in both animal and human work (Andersen, Thompson, Krenzel, & Teicher, 2002; Lidow & Rakic, 1992; Montague, Lawler, Mailman, & Gilmore, 1999; Seeman et al., 1987). However, some studies have suggested that DA receptor densities decline in dorsal, but not ventral striatum (where levels remain the same) over adolescence (Teicher, Andersen, & Hostetter, 1995).

Research on DA transporters have been inconsistent in the midbrain (VTA and substantia nigra) with research showing no consistent developmental change (Moll et al., 2000), increases over adolescence (Galineau, Kodas, Guilloteau, Vilar, & Chalon, 2004), and peaks in late childhood (Coulter, Happe, & Murrin, 1996). Other research has suggested that in striatum including NAcc, DA transporter levels increase into late childhood and remain stable into adolescence (Coulter, et al., 1996; Galineau, et al., 2004; Tarazi, Tomasini, & Baldessarini, 1998). Lastly, evidence has suggested that COMT activity is also increased in adolescence in human PFC as well as porcine striatum, relative to adults (Brust et al., 2004; Tunbridge et al., 2007).

Investigators have posited that the overall pattern of DA signaling in adolescence indicates that the DA system may be at a "functional ceiling" relative to childhood or adulthood (Chambers, et al., 2003) and that DA related responses in adolescence may be heightened, due to peaks in midbrain DA cell firing and synaptic availability. As PFC function becomes more efficient during the adolescent stage, changes in the density and function of D_1 and D_2-like receptors refine and balance excitatory and inhibitory responses (Tseng & O'Donnell, 2005), increasing signal to noise. Tonic levels of DA are elevated in adolescence, which may result in inefficient regulation of phasic signaling in response to rewards (Luciana, et al., 2012). Although, see Paus et al., (2008) for a counter argument.

Prior studies have demonstrated that adolescent rodents exhibit increased reinforcing effects to drugs that involve DA function such as alcohol, nicotine, amphetamines, and cocaine (Adriani, et al., 1998; Adriani & Laviola, 2000; Badanich, et al., 2006; Brenhouse & Andersen, 2008; Frantz, O'Dell, & Parsons, 2007; Laviola, Adriani, Terranova, & Gerra, 1999; Mathews & McCormick, 2007; Shram, et al., 2006; Varlinskaya & Spear, 2010), and demonstrate increased

sensitivity to DA receptor antagonists (L. P. Spear & Brake, 1983; L. P. Spear, Shalaby, & Brick, 1980; Teicher et al., 1993). Interestingly and perhaps facilitating adolescent's sensitivity to rewarding effects of drugs, evidence suggests that adolescents demonstrate *decreased* aversive response to substances of abuse (i.e. milder withdrawal responses, reduced psychomotor effects) (Doremus, Brunell, Varlinskaya, & Spear, 2003; E. D. Levin, Rezvani, Montoya, Rose, & Swartzwelder, 2003; L. P. Spear, 2002) concurrent with the pleasurable outcomes (Adriani, et al., 1998; Adriani & Laviola, 2000; L. P. Spear & Brake, 1983).

Based on the inverted-U model of DA functioning in PFC and striatum, it is possible that with immaturities in DA function, adolescents have a vulnerability to surpass the threshold needed for optimal functioning (Wahlstrom, Collins, et al., 2010; Wahlstrom, White, et al., 2010). Earlier maturation of subcortical systems relative to prefrontal (Casey, et al., 2008), and an imbalanced shift in the adolescent brain that is more "go" oriented with less amygdala and cortical - mediated "no-go" regulation (Chambers, et al., 2003; Ernst, et al., 2006), it is further possible that these thresholds differ by brain region. However, maturational changes in the DA system have not mapped directly onto immaturities in incentive-driven behaviors in adolescence, suggesting that a more comprehensive examination of the interaction of various *aspects* of the DA system (receptors, clearance, innervation etc…) that directly alter behavior (Luciana, et al., 2012; L. P. Spear, 2011).

Altered DA function in adolescence is interesting for several reasons: First, DA neurotransmission supports reinforcement learning as it tunes the strength of synapses, thereby controlling plasticity. Second, DA projections from VTA to both striatal and prefrontal structures have been implicated in affective and motivated behaviors, which are altered in adolescence.

Lastly, DA transmission is highly implicated in the pathophysiology of neuropsychiatric disorders that often emerge in adolescence (e.g. schizophrenia, drug abuse).

However, there exists a considerable amount of inter-individual variability in DA function, mediated by genetic and environmental factors that likely underlie variability in traits that lead to individual differences in risk-taking behaviors. Indeed the majority of adolescents do not engage in life-threatening risk-taking behaviors or develop psychiatric disorders. Based on the inverted-U dose-response model of DA functioning in PFC, Wahlstrom et al., (2007) proposed a model suggesting that genetically driven variability in DA-related behavioral functioning may be shifted in adolescents relative to adults. Individuals with relatively lower levels of DA activity (left hand limb of the curve) will shift upward during adolescence, but will remain relatively lower than adolescents with relatively intermediate DA levels, who may function at more optimal levels of DA related functioning (i.e. adaptive novelty exploration). Individuals with high baseline levels may be pushed to excessive levels that lead to suboptimal behaviors (i.e. risk taking) (Luciana, et al., 2012). Furthermore, these biological predispositions to behavior will result in individual differences in learning and experience over adolescence, which will influence behavioral variability in adulthood.

Extending this model, that variability in midbrain DA levels across individuals may help explain how changes in DA related functioning places individuals at differing locations on the inverted-U model, we propose that adolescents may overall show immature levels of striatal/PFC related functioning and lie on a different curve that is shifted downwards (suboptimal). This is a model focused on the role of DA but we recognize that immaturities in the brain independent from DA may also contribute to relative changes in the adolescent brain and. Adolescents will further demonstrate intra-group variability with respect to DA function that is distinct from

adults (Figure 1), with individuals with relatively high baseline DA shifting to the right of the curve (suboptimal functioning) in adolescence before stabilizing into adulthood. Conversely, individuals with *low* baseline DA, may show relatively improved brain function in adolescence before decreasing to the left hand limb of the curve in adulthood. In other words, we propose that inherent (e.g., genetic) DA variability will be expressed differently in adolescence and adulthood. Although highly simplistic, this model highlights that inter-individual variability in brain function (and by extension behavior) as a function of DA signaling may be distinct in adolescence relative to adulthood.

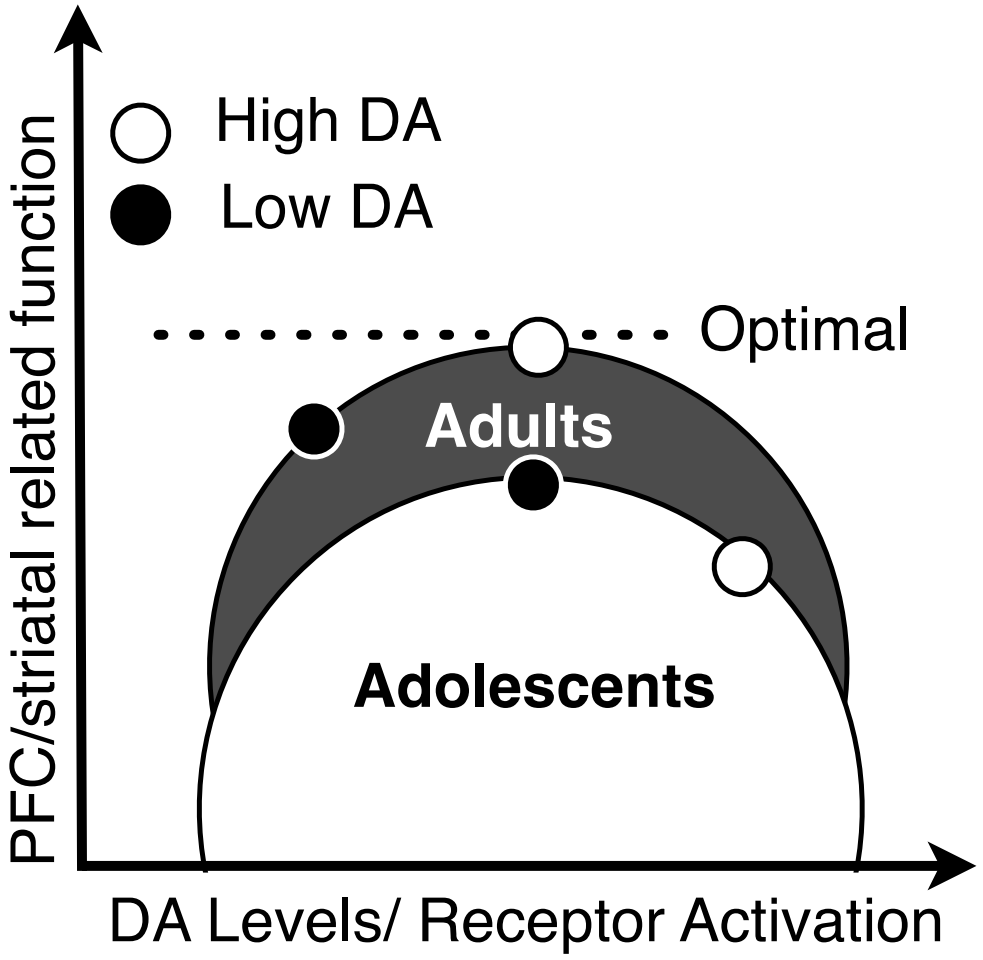

Figure 1. Predicted Model of Adolescent Brain Function Modulated by DA

A simplistic extension of the putative "inverted-U" shaped dose response curve of dopamine function relative to cognitive performance in adolescence (Wahlstrom et al., 2007). We predict that adolescents will lie on their own curve, below adult levels of "optimal" due to continued immaturities in brain function. Furthermore, individuals with *increased* baseline DA function or basal mesoaccumbens DA activity, who are purported to be closer to optimal in adulthood, may lie outside the optimal range in adolescence. Conversely, individuals with relatively decreased levels of DA may sit closer to the top of the curve in adolescence when DA levels are purportedly higher.

1.6 DEVELOPMENTAL IMAGING GENETICS

Given that the DA system undergoes considerable reorganization over the adolescent period, an important next step is to understand the influence of these changes on brain function over adolescence. Methodologically, studying neurotransmitter systems in human development is challenging, as pharmacological and other invasive procedures (i.e. PET) cannot be used in human subjects under the age of 18. In an effort to develop biologically plausible and testable hypotheses on the influence of DA function on brain function, recent efforts have focused on identifying variants in the human genome that directly impact protein function and subsequently cellular and systems-level function. Given the hypothesized vulnerabilities of the immature adolescent system, the variability of which may be modulated by dopamine availability and transmission, studying the influence of genetically-driven variability of dopamine function over development has great potential to elucidate biological basis of individual differences in behavior as well as identifying etiologies of psychopathology

In recent years, researchers have combined variations in candidate genes with known functional significance with neuroimaging measures as an intermediate phenotype approach to link genes to behavior (Hariri & Weinberger, 2003). This approach is based on the notion that the influence of genetic variation on behavior is likely mediated by changes in cellular and systems levels of functioning in the brain. Indeed, the study of the influence of genetic variation on brain function or “imaging genetics” has provided considerable insight on the influence of

genetically driven variability on brain physiology underlying individual differences in information processing (e.g. (Brown & Hariri, 2006; Drabant et al., 2006; Hariri & Lewis, 2006; Hariri & Weinberger, 2003)) (Figure 2). Allelic variations in genes that code for DA proteins and alter the function of the protein may result in alterations in DA availability, which can have an impact on behaviorally relevant neural activity (Aarts et al., 2010; Bertolino, Blasi, et al., 2006; Drabant, et al., 2006; Dreher, et al., 2009; Yacubian et al., 2007). However see: (Flint & Munafo, 2007; Kendler & Neale, 2010; Walters & Owen, 2007) for arguments and opposing views and considerations of this approach.

Variation within DA genes that code for the various dopamine receptors (*DRD1*, *DRD2*, *DRD3*, *DRD4*, *DRD5*), DA transporter (*DAT1*), and DA degradation enzymes such as monoamine oxidase (*MAOA*) and catechol-o-methyltransferase (*COMT*) have been associated with individual differences in personality traits such as risk seeking and neuroticism, cognitive control and reward processing, drug abuse, and the etiology of several neuropsychiatric disorders such as schizophrenia, ADHD and Parkinson's disease (Eley, Lichtenstein, & Moffitt, 2003; Enoch, Schuckit, Johnson, & Goldman, 2003; Karayiorgou et al., 1997; S. S. Lee et al., 2007).

Given the known changes in the DA system in adolescence and key maturational changes in brain function over adolescence, imaging genetics may provide a better understanding the role of dopamine on a developing brain system and the basis of inter-individual variability in risk-taking behaviors. In the following sections we focus on neuroimaging studies of common functional polymorphisms or variants in key DA genes that have been extensively studied in the context of motivated behaviors in frontostriatal circuits. We will focus on neuroimaging studies as an intermediate phenotype between genes behavior. Studies of behavioral associations with

DA genes have been reviewed in depth elsewhere (e.g. (Nemoda, Szekely, & Sasvari-Szekely, 2011)) and will not be a focus of the current review.

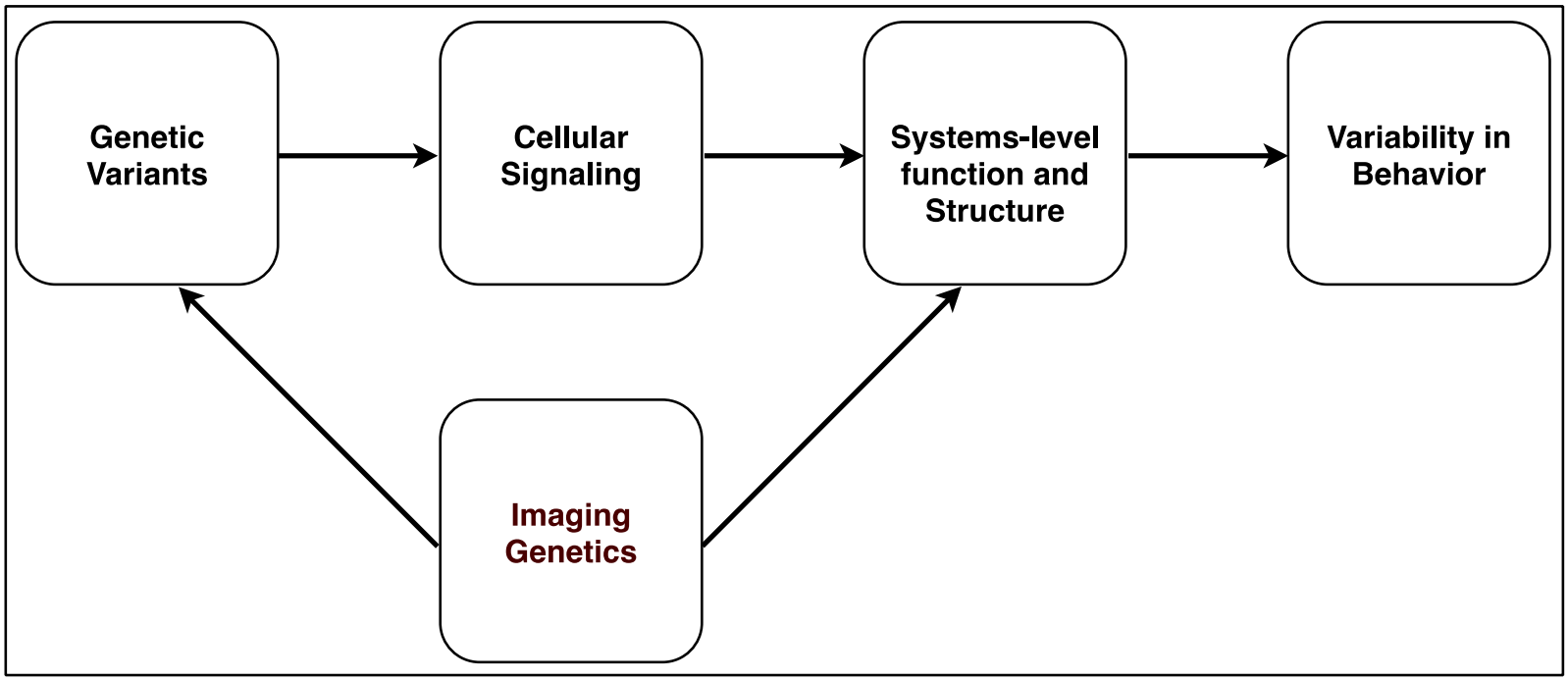

Figure 2. Schematic of Imaging Genetics

Imaging genetics is a promising methodology for studying how variation in functionally relevant genes can influence variability in behavior through alterations in cellular and systems-level brain function. Genes with known functional significance alter resulting proteins, which influence cellular signaling. Changes in cellular signaling consequently can alter function within and between brain structures. Changes in brain function can directly influence resulting behaviors

1.6.1 DA Receptor Genes

The presence of both D_1- and D_2-like receptors in the brain result in a complex balance of excitatory-inhibitory signaling and exerts a strong influence on frontostriatal function and connectivity. The genes that code for these five main receptor subtypes are *DRD1*, *DRD2*, *DRD3*, *DRD4* and *DRD5* respectively. In the PFC, D_1 receptors act on glutamatergic pyramidal cells, increasing task related firing (Farde, et al., 1987; Goldman-Rakic, 1990; Lidow, et al., 1991). Simultaneously, D_1 receptor activation on local GABAergic (inhibitory) interneurons serves to inhibit irrelevant glutamatergic inputs (Durstewitz, Seamans, & Sejnowski, 2000). D_1 and D_2 receptors have complementary roles, with tonic stimulation of D_1 receptors allowing for maintenance on information online and stabilization of functional states, and D_2 receptor binding involved in flexible updating of information and allowing for the transition between functional states (Durstewitz & Seamans, 2002; Seamans, et al., 2001; Seamans & Yang, 2004).

Limited research has examined polymorphisms of the D_1-receptor gene (*DRD1*) in relation to brain structure/function. One study demonstrated altered prefrontal-parietal functional connectivity in schizophrenic patients during working memory genotyped for the *DRD1* DdeI polymorphism (Tura, Turner, Fallon, Kennedy, & Potkin, 2008). AG heterozygotes (with presumably increased D_1 receptor function) engaged the DLPFC more than AA homozygotes, who engaged a more widely distributed circuitry.

The D_2 receptor, which is expressed more abundantly in striatum relative to PFC, exerts a strong influence on frontostriatal connectivity through both inhibition of excitatory and disinhibition of inhibitory connections (Cepeda & Levine, 1998; Goto & Grace, 2005). D_2 receptors have two distinct isoforms, the short isoform (D_2-S) acts mainly as a presynaptic

autoreceptor, inhibiting DA release, whereas the long isoform (D_2-L) primarily functions to inhibit the post synaptic cell (Centonze et al., 2003). A specific ratio of both isoforms is necessary for efficient DA modulation of both inhibitory GABAergic striatal neurons as well as inhibition of glutamatergic function in PFC. Decreased D_2 autoreceptor function serves to increase DA release and individuals with decreased D_2-S demonstrate increased novelty-seeking and DA release and reward reactivity (Pecina et al., 2012; Zald, et al., 2008).

Polymorphisms in the gene that codes for the D_2 receptor (*DRD2*) influence mRNA transcription of the protein, and ultimately its function have been identified including, −141 C Ins/Del, Ser311Cys, Taq1A ANKK1, Taq1B, C957T, rs12364283, rs2283265 and rs1076560 (Zhang et al., 2007). Polymorphisms that result in increased D_2-S (e.g. rs1076560 G allele, rs2283265 G allele, rs4274224 A allele,) increase DA uptake and demonstrate increased cortical efficiency during working memory (Bertolino, et al., 2009; Zhang, et al., 2007), increased prefrontal to striatal effective connectivity (Tan et al., 2012), and decreased reward reactivity in striatum and PFC (Pecina, et al., 2012) relative to individuals with increased D_2-L. Decreased reactivity to reward in individuals with less D_2 autoreceptors may be due to an inhibition of DA release into striatum.

1.6.2 Functional Polymorphism in the *COMT* Gene

Catechol-O methyltransferase (COMT) a major enzyme for catecholamine catabolism is vital to regulating DA turnover in the PFC where DA transporters are scarce (Hong, Shu-Leong, Tao, & Lap-Ping, 1998; Matsumoto et al., 2003)., which has been shown to steadily *increase* over adolescence. A single nucleotide polymorphism (SNP) resulting in a methionine (*met*) to valine

(*val*) substitution at codon 158 of the gene that codes for the COMT enzyme (*COMT)* results in a significant change in protein function (Tunbridge, 2010). The *COMT val* allele is associated with high enzymatic activity and consequently low synaptic dopamine levels in PFC, whereas the *COMT met* allele has lower thermostability and lower activity at physiologic temperatures resulting in approximately one third less enzyme activity and consequently high synaptic dopamine in the PFC (Chen et al., 2004). Heterozygotes with one copy of each allele show intermediate levels of *COMT* activity in the PFC. Despite a predominant expression in PFC, the *COMT val158met* polymorphism may have downstream effects on midbrain DA neurons, with the *val* allele, which results in decreased prefrontal DA increases DA production/release in midbrain relative to the *met* allele (Meyer-Lindenberg, Kohn, Kolachana, Kippenhan, Inerney-Leo, et al., 2005). *COMT val158met* has been widely associated with prefrontal function specific to tasks dependent on DA neurotransmission (Bilder et al., 2002; Diamond, Briand, Fossella, & Gehlbach, 2004; Egan et al., 2001; Goldberg et al., 2003; Malhotra et al., 2002; Mattay et al., 2003) including working memory, response inhibition, set shifting and reward processing.

Studies have demonstrated more efficient cortical function in individuals with the *met* allele relative to *val* (e.g.(Egan, et al., 2001; Mattay, et al., 2003; Meyer-Lindenberg, Kohn, Kolachana, Kippenhan, Inerney-Leo, et al., 2005)) as well as differences as a function of *COMT* genotype on brain function related to reward and affective processing (Drabant, et al., 2006; Dreher, et al., 2009; Yacubian, et al., 2007). Furthermore, increasing DA levels (through pharmacological manipulations) has been shown to differentially influence frontostriatal brain activity (in parallel with cognitive performance) as a function of *COMT val158met* genotype (Apud et al., 2007; Mattay, et al., 2003), with *met* individuals demonstrating diminished cortical efficiency during tasks of cognitive control and *val* demonstrating improvements.

Limited research has examined the influence of the *COMT val158met* polymorphism over adolescence. Dumontheil et al. (2011), using a hybrid longitudinal/cross sectional study spanning 6 to 20 years of age, demonstrated that brain activity during a visuo-spatial WM task in frontal and parietal regions were increased in activity across age only for individuals homozygous for the *val* allele, but not *met* carriers, suggesting perhaps a compensatory mechanism in *val* adolescents for relatively worse performance on the task. *Val*/*val* homozygotes also show slower cortical thinning over adolescence in posterior parietal cortex, perhaps reflecting slower pruning and thereby increased inefficiency in cortical processing. To date, this is the first fMRI study examining the influence of the *val158met* polymorphism on brain function and structure from childhood to adulthood. *COMT* effects in adolescence have also been found in studies of structural and connectivity (Thomason et al., 2010; Thomason, Waugh, Glover, & Gotlib, 2009), suggesting that variability in prefrontal DA availability may have an impact not only within brain regions, but also in the connections between them and that these differences may be present across development.

Taken together these findings suggest that there may be an interaction between peak DA availability, age and genetic variability with a unique profile in adolescence and that *COMT* is an especially promising candidate gene to elucidate the influence of DA over development. It is also important to note that as catecholamine processor, *COMT* is also responsible for catabolizing norepinephrine, which has been previously shown to steadily increase from childhood to adulthood (Goldman-Rakic & Brown, 1982), although imaging genetics research to date has focused solely on the influence of *COMT* on DA function.

1.6.3 Functional Polymorphism in the *DAT1* Gene

The DA transporter (DAT) is responsible for taking back DA from the synapse into the presynaptic neuron. The human DAT is abundantly expressed in the striatum and involved in synaptic DA reuptake and clearance (Jaber, Bloch, Caron, & Giros, 1998). A variable number of tandem repeats in the gene that codes for DAT (*DAT1* or *SLC6A3*) most commonly results in alleles between 3 and 13 repeats of a 40-base pair sequence in its 3' untranslated region (Vandenbergh et al., 1992) as coding region variants are quite rare. The DAT binding site density for the most common repeat alleles (9R and 10R) is significantly less (50%) for the 9R allele is significantly (50%) less than the 10R allele, linking the 9R allele with reduced DAT expression and greater striatal synaptic DA (Fuke et al., 2001; Mill, Asherson, Browes, D'Souza, & Craig, 2002; VanNess, Owens, & Kilts, 2005), although some studies have demonstrated the opposite (Mill, et al., 2002; van de Giessen et al., 2009).

Lower DAT expression may reduce synaptic DA clearance thereby increasing both tonic and phasic DA levels (Cagniard, Balsam, Brunner, & Zhuang, 2006; Cagniard et al., 2006). Evidence relating *DAT1* to reward reactivity is mixed, with some studies demonstrate an increase in reactivity to rewards in 9R carriers (Dreher, et al., 2009; Forbes, et al., 2009; Yacubian, et al., 2007) and one study demonstrating a positive correlation between NAcc reactivity and trait reward sensitivity in only the 10/10 homozygotes.

Although DAT is primarily expressed in striatum, the DA mediated connections between PFC and striatum may have upstream influence on prefrontal activation. Studies have demonstrated that the *DAT1* 3'-VNTR polymorphism modulates brain function underlying cognitive flexibility with individuals carrying 9R demonstrating increased NACC and dorsomedial PFC activity during working memory updating and task switching (Aarts, et al.,

2010; Garcia-Garcia, Barcelo, Clemente, & Escera, 2010) and increased PFC activity during inhibitory control (Congdon, Constable, Lesch, & Canli, 2009; Congdon, Lesch, & Canli, 2008).

Due to its impact on DA availability in striatum, the *DAT1* 3'-VNTR, has been of specific interest in understanding psychopathology, but primarily Attention Deficit Hyperactivity Disorder (ADHD) (Durston, de Zeeuw, & Staal, 2008). Developmental studies using the *DAT1* polymorphism have demonstrated that typically developing adolescents with the 10R allele perform poorer on cognitive control tests (Cornish et al., 2005) and demonstrate differential recruitment of prefrontal and striatal regions during tests of inhibitory control (Braet et al., 2011).

1.6.4 Functional Polymorphism in the *MAOA* Gene

The Monoamine Oxidase A (*MAOA*) gene (MIM 309850) is located on chromosome Xp11.23 and encodes the enzyme *MAOA*. *MAOA*, which is predominately found in catecholaminergic neurons all over the brain, is responsible for degrading monoamine neurotransmitters (including DA, norepinephrine, and serotonin). A VNTR polymorphism of 30 base-pairs in the upstream promotor region (*MAOA* u-VNTR), influences transcriptional efficiency (Sabol, Hu, & Hamer, 1998). Individuals with 3.5 or 4 repeats have been associated with having relatively higher *MAOA* expression (*MAOA*-H) relative to 3 or 5 repeats (*MAOA*-L) (Deckert et al., 1999; Sabol, et al., 1998). *MAOA* has been widely studied in the context of affective related processing due to its influence on serotonin availability with lower *MAOA* binding being associated with aggression and impulsivity (Alia-Klein et al., 2008; Brunner, 1996), and higher *MAOA* binding associated with depression (Meyer et al., 2006). Less attention is given to *MAOA* regarding its

influence on DA although research suggests that there is an moderating effect of the u-VNTR polymorphism on DA-related function (and dysfunction) in the brain (Alia-Klein et al., 2011).

Furthermore, studies have demonstrated an influence of *MAOA* on DA rich areas with the *MAOA*-L allele associated with decreased prefrontal activation during response inhibition (Passamonti et al., 2008) and conflict resolution (Fan, Fossella, Sommer, Wu, & Posner, 2003). *MAOA*-L is also associated with increased activation of amygdala in response to affective stimuli concurrent with decreased ACC and OFC activity (B. T. Lee & Ham, 2008; Meyer-Lindenberg et al., 2006) and increased fronto-limbic connectivity (Buckholtz et al., 2008; Dannlowski et al., 2009). Adolescents demonstrated atypical brain activity as a result of peer rejection in ventro-lateral PFC and as a function of *MAOA* genotype in amygdala. It is important to note that although the *MAOA* gene is located on the X chromosome, prior studies have shown an additive effect of the alleles with female heterozygotes showing intermediate activity to both male hemizygotes and female homozygotes (Eisenberger, Way, Taylor, Welch, & Lieberman, 2007; Meyer-Lindenberg, et al., 2006; Prom-Wormley et al., 2009).

1.6.5 Gene-Gene Interactions

Gene influences on brain physiology do not occur in isolation. For example an individual homozygoes for the *COMT* met allele who is also homozygoes for the *DAT1* 10R allele and have the *DRD2* Taq1A A1 allele, may have a distinct brain phenotype relative to an individual who has another combination of alleles across genes, leading to infinite combinations of genetic variability that may have a significant influence on brain function. In addition, allelic variation in one gene may exacerbate or alleviate the influence of another gene (a phenomenon called

epistasis). Indeed, studies have demonstrated effects on brain activity as a function of interactions between genes during cognitive tasks (Bertolino, Blasi, et al., 2006; Bertolino et al., 2008; Dreher, et al., 2009; Yacubian, et al., 2007). For example, prior studies found additive effects of *COMT* and *DAT1* during the reward anticipation and outcome stages of reward processing in both PFC and striatum (Dreher, et al., 2009; Yacubian, et al., 2007).

More recently, research groups have explored the influence of several DA genes on brain circuitry during reward processing using a "multilocus composite score" (Plomin, Haworth, & Davis, 2009), assigning each participant a single additive score of relative levels of DA signaling. The idea behind this approach is that although individual loci likely account for a very small proportion of the variance in brain function, especially in smaller samples of participants, combining multiple *functionally relevant* genes through a cumulative profile score may increase the amount of variability explained. Prior research using this approach has found an effect of ventral striatal reactivity (Nikolova, Ferrell, Manuck, & Hariri, 2011), caudate, and putamen (Stice, Yokum, Burger, Epstein, & Smolen, 2012) as a function of the composite score during receipt of monetary rewards, although (Stice, et al., 2012) failed to replicate an effect in ventral striatum. To date, no studies have been conducted to look at the influence of multiple functional polymorphisms in DA genes in the PFC or *across* adolescence.

1.7 SUMMARY AND IMPLICATIONS

Neurodevelopmental studies indicate a protracted development through adolescence of brain systems including PFC (PFC) and the striatum. These systems support motivationally driven behaviors and may contribute to vulnerabilities in the emergence of psychopathology. The PFC

and striatum are believed to support cognition and motivation through their unique interconnectivity, including inhibitory control of striatum by PFC neurons and reciprocal striatal efferents to PFC.

Dopamine (DA) availability is increased during the adolescent period in human and animals and may be an adaptive mechanism for enhancing novelty seeking to gain skills of independence that support adult survival as well as play an important role in the emergence of neuropsychiatric disease. In adults, the relationship between cortical DA levels and executive function is suggested to follow an inverted U shaped curve, with either too little or too much DA associated with relatively worse PF function than intermediate levels. Exaggerated DA levels in both striatum and PFC in adolescence may result in an increased sensitivity to rewards coupled with poor executive regulation of impulse driven behaviors increasing vulnerabilities to risk-taking behavior. In addition to immaturities in brain function during the adolescent period, is the presence of great variability in behavior, and in the etiology of psychiatric disorders that emerge in adolescence. This generates questions about the biological mechanisms that underlie this variability, a line of research yet to be explored. We propose a developmental model of expression of DA variability that indicates that given the interaction between a reorganization of the DA system in adolescence as well as the variability in genetic predisposition for DA availability, the relationship between DA and brain function will be unique in adolescence relative to adulthood.

The association between basic biological variants and variability in behavior is an increasing field of study. Fundamental to this approach is the idea that multiple levels of organization influence brain function. Gene expression is one of the primary sources of variability, acting through cellular and system-level neural processes to produce the complex phenomena that

manifest in behavioral function and dysfunction. Investigating variability influenced by genetic factors in a developing system can provide insight into biological mechanisms by which individual differences in brain function underlying risk taking and vulnerability for psychopathology emerge. Studying the effects of genetically driven variability in DA-dependent brain regions with imaging genetics allows us to target *behaviorally relevant* neural systems that demonstrate persistent immaturities in adolescence with a significant increase in power to detect age-related changes. This approach is contingent on the idea that adolescents' abilities to modulate cognitive control through reward processing are still immature, reflected by a greater influence of incentives on behavior and differential recruitment of reward-related circuitry compared to adults. The rationale for developmental imaging genetics studies is that, with its incisive methodological tools and its capacity for deriving detailed structural and functional information, brain imaging holds particular promise for linking the effects of genes on behavior. An integrative neuroscience approach, combining genes with systems-level functional and structural neuroimaging will allow investigators to make 1) associations between genetic variants and behaviorally-relevant neural systems and 2)inferences about resulting behavioral implications, within a framework of adolescent development.

Taken together, evidence indicates that the adolescent period is a stage of increased sensation seeking with a unique brain signature. However, inherent variability in genetic predisposition as well as environmental influences can modulate the expression of the predisposition to be sensation seeking which can sometimes lead to risk-taking behavior. This dissertation seeks to examine the moderating role of genetically mediated DA availability on frontostriatal brain function in adolescence. As described above, we are interested in both *tonic* and *phasic* DA signals, both of which have strong influence on motivated behaviors and may play distinct and

influential roles in adolescent brain function. To this end, our first study was to examine the integrity of frontostriatal networks using resting state functional connectivity (Chapter 2). This methodology allows us to examine intrinsic connections between brain regions by correlation low frequency fluctuations in fMRI time-series signals, which may be modulated by *tonic* DA transmission. We then look more directly at the role of frontostriatal brain function on incentive-driven behaviors using a rewarded inhibitory control task that has a known developmental signature (Geier & Luna, 2011), the responses during which may be modulated by *phasic* DA signaling (Luciana, et al., 2012) (Chapter 3).

2.0 INFLUENCE OF SYNAPTIC DA AVAILABILITY ON INTRINSIC FRONTOSTRIATAL FUNCTIONAL CONNECTIVITY OVER ADOLESCENCE

2.1 INTRODUCTION

Donald Hebb postulated in 1949: “cells that fire together, wire together” (Hebb, 1949). Fast forward forty or so years and the advent of functional MRI techniques have allowed researchers to examine *intrinsic* brain networks with the idea that neurons that stay connected during rest are also synchronous during task (Biswal, Yetkin, Haughton, & Hyde, 1995; Fox, Corbetta, Snyder, Vincent, & Raichle, 2006). Resting state functional connectivity (rsFC) involves correlating slow fluctuations (< 0.1 Hz) in blood oxygen level dependent (BOLD) time series between brain regions in the absence of performing an explicit task. To this end, it allows for evaluation of interregional coherence in neural activity, and has been used in several domains to examine systems level organization of task-specific as well as default-mode networks (Cordes et al., 2001; Cordes et al., 2000; Fox, et al., 2006; Lowe, Mock, & Sorenson, 1998; Xiong, Parsons, Gao, & Fox, 1999). It is important to note that rsFC (and even task based functional connectivity) does not necessarily reflect direct excitatory anatomical connections; rather it is a measure of the statistical likelihood of different brain areas to be simultaneously active, allowing for network integrity and important synaptic connections to be sustained (Fox & Raichle, 2007).

Prior studies of frontostriatal rsFC using seed-based techniques have demonstrated important functional distinctions between regions in striatum that are strongly connected to regions of the PFC (Di Martino, et al., 2008). Frontostriatal connections have been long thought to be organized by rostral/caudal, (dorsal/ventral), lateral/medial divisions (Alexander, et al., 1986; Kemp & Powell, 1970; Postuma & Dagher, 2006), with dorsal/caudal aspects of striatum (i.e. caudate, putamen) connected to dorsal/lateral aspects of PFC and ventral striatum (NAcc) to ventral/medial areas of PFC.

A brain-wide reorganization in task-based and resting functional connectivity has been extensively studied over adolescence, showing both increases and decreases in connectivity between frontal and striatal areas (Christakou, Brammer, & Rubia, 2011; N. U. Dosenbach et al., 2010; Supekar et al., 2010). In addition, as DA signaling is critical for modulating communication within frontostriatal circuits, studies have also demonstrated alterations in functional connectivity as a function of DA availability in adulthood, demonstrating both increases and decreases as function of increasing DA (Flodin, Gospic, Petrovic, & Fransson, 2012; Honey et al., 2003; C. Kelly et al., 2009; Kwak et al., 2010). However, to date, no studies have examined how DA availability may moderate developmental changes in the functional organization of the brain.

To this end, this chapter examines the development of rsFC over adolescence as a function of allelic variations in genes that code for DA *clearance* proteins, that is proteins that are involved in synaptic and extrasynaptic DA removal and degradation. We selected loci based on prior links with both changes in DA function as well as known associations with changes in frontostriatal circuitry: The *COMT val158met* polymorphism, the *DAT1* 3'-VNTR, and the *MAOA u*-VNTR. As described in the introduction, The *COMT val158met* polymorphism

(rs4680) in the third exon of the *COMT* gene, which is associated with changes in enzymatic degradation of extracellular DA primarily in the PFC (Chen, et al., 2004), has been widely studied in the context of frontostriatal circuitry (Bilder, et al., 2004), and has demonstrated an effect on brain signaling across age groups (e.g. (Dumontheil, et al., 2011)). The *MAOA u*-VNTR, located on the X chromosome, has been predominately associated with affective-related brain processing, specific to frontostriatal circuitry, having a functional influence on monoamine (including DA) degradation all over the brain (Sabol, et al., 1998). Finally, the *DAT1* VNTR, in the 3' untranslated region of the DAT gene (SLC6A3), which influences DA reuptake predominantly in striatum has been associated with changes in striatal signaling (e.g. (VanNess, et al., 2005). Lastly, using the methods of Nikolova et al., (2011), we combined the relative scores in each of these polymorphisms within each individual, to create a multilocus composite score to explore a cumulative effect of these loci on frontostriatal connectivity over adolescence. We did not examine the role of DA receptor genes in the current study because less is currently known about the specific functional significance at the protein level of receptor gene polymorphisms relative to the three loci we chose. In addition, we wanted to restrict our analyses to genes that coded for extracellular DA clearance proteins rather than combine both clearance and receptor genes which may have differing effects on the DA system and on brain function as a whole, making findings more difficult to interpret. Finally, our sample size limited us to choosing few loci, which made choosing functionally relevant and highly studied candidate genes of particular importance.

We predicted that overall, there would be changes in frontostriatal connectivity over adolescence in line with prior research (N. U. F. Dosenbach et al., 2010; Supekar, Musen, & Menon, 2009). Extending from our overall predicted model from Chapter 1 (Figure 1), we

predicted a number of different patterns of connectivity as a function of age and genotype as depicted in Figure 3.1. First, given the hypothesized *peaks* in midbrain DA neuron activity (which by extension may overall increase synaptic DA availability), we may observe a quadratic peak in connectivity over adolescence that is moderated by individual differences in genetic variability (Figure 3.2). Second, some connections (i.e. motor control circuits) may not show any age-related changes but show an effect of genotype that is consistent across age, suggesting a rank-order stability. Third, we may see linear changes across age, preserving rank-order stability of the effect of genotype such that certain circuits show the same genetically driven variability earlier in adolescence relative to early adulthood (Figure 3.3). Lastly, Figures 3.4 and 3.5 depict age by genotype interactions that show differential variability as a function of genotype earlier in adolescence relative to later, with connectivity differences either converging into adulthood as maturational events render circuits more stable (Figure 3.4) or switch over adolescence (Figure 3.5).

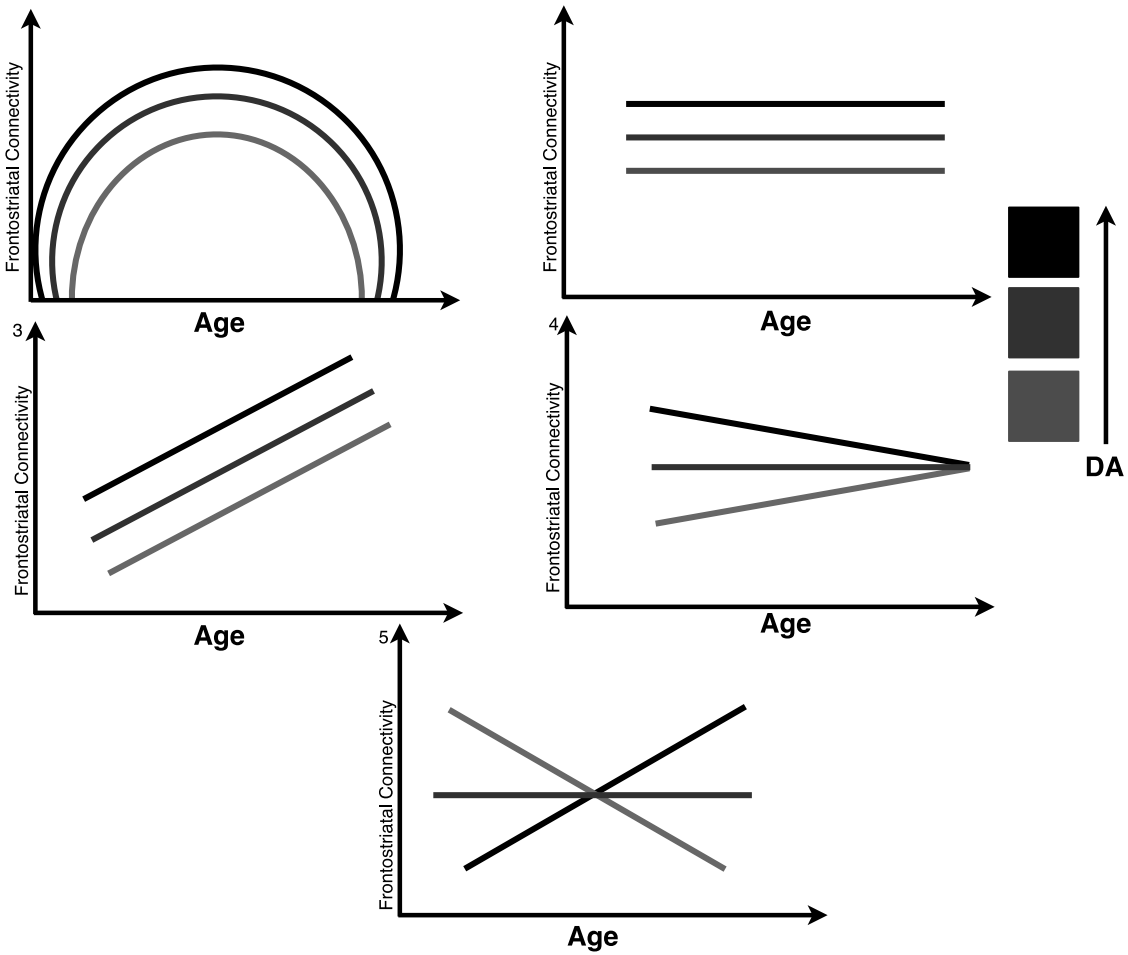

Figure 3. Predicted patterns of age by genotype effects on frontostriatal functional connectivity.
On the x-axis is age and y-axis is connectivity strength. Darker lines signify *increased* DA availability relative to lighter gray lines. DA = Dopamine

2.2 METHODS

2.2.1 Participants

A total of 167 participants between the ages of 10 and 20 were recruited as part of a larger longitudinal study. Of those participants, 111 were used in the current resting state analyses. The remaining participants were excluded from the current study because of 1) lack of genetic data, 2) Too much head movement 3) No resting state scan was conducted during the scanning session, and 4) Unreliable peripheral physiological data, which was required for preprocessing of the resting state data (described below), and 5) Participants were not of Caucasian descent, which was necessary to avoid stratification effects and maintain allele frequency distributions that are comparable with the population. All participants had (corrected or uncorrected) visual acuity of at least 20/40 and no medical history of psychiatric neurological disease or injury and no first degree relative with a psychiatric illness as determined by interview. 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. Table 2.1 shows the breakdown of participants by genotype. Figure 4 shows the genotype distributions in two-three year age bins. There were no differences in mean age p's > .05 or IQ scores across groups (p's > .05).

Table 1. Breakdown of participants by genotype

Gene		N 111	% females	Mean Age 10-20	WASI 2
COMT	Met/Met	34	29	15.17(2.97)	112.92(8.29)
	Val/Met	50	64	14.77(2.96)	107.84(11.26)
	Val/Val	26	69	16.06(2.67)	110.35(11.85)
MAOA	3R	27	67	15.52(2.84)	111.29(11.38)
	3R/4R	26	100	16.03(2.86)	110.25(9.77)
	4R	57	58	14.58(2.89)	108.25(11.10)
DAT1	9R	54	54	14.95(2.98)	108.48(11.18)
	10R/10R	56	55	15.52(2.84)	110.83(10.43)
Multilocus	3.0	14	43	15.11(2.70)	108.69(10.01)
Composite	2.5	14	57	15.24(3.00)	110.65(11.30)
	2.0	36	53	14.94(2.68)	109.22(11.04)
	1.5	23	57	15.49(3.18)	111.46(9.78)
	1.0	12	83	15.51(3.27)	109.14(12.48)
	0.5	11	36	15.28(2.32)	105.00(10.07)

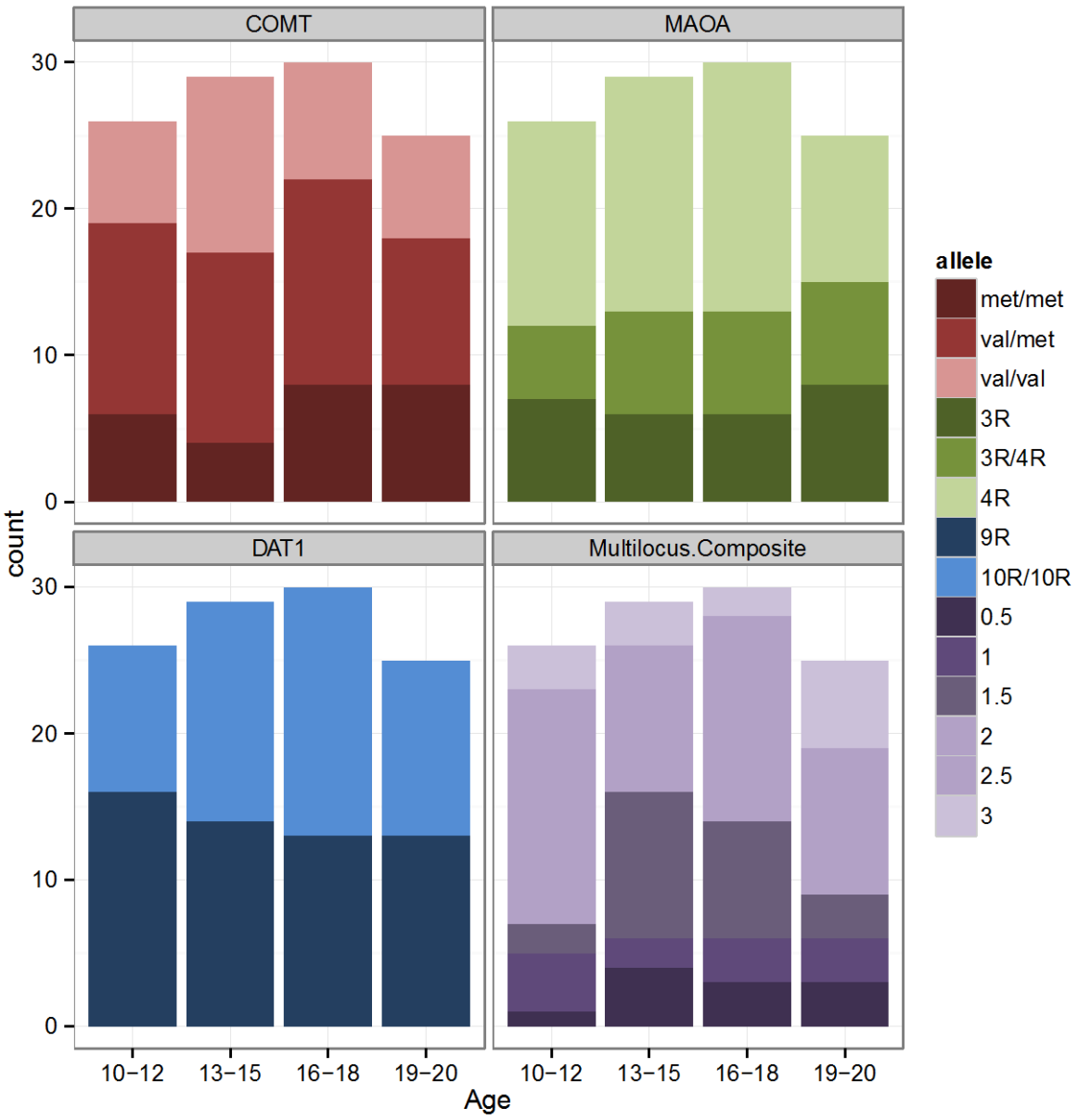

Figure 4. Genotype distributions across age

2.2.2 Genotyping

High molecular weight DNA was isolated and extracted from saliva obtained using the DNA Genotek Oragene kits (DNA Genotek: Kanata, Canada). Using allele specific primers, samples were genotyped for the *COMT* val158met polymorphism (rs 4680) gene using polymerase chain reaction (PCR) following a previously published protocol (Kunugi et al., 1997). Genotyping of the *MAOA u*-VNTR was also done using PCR, following the protocol published by (Sabol, et al., 1998). Genotyping for the *DAT1* 3' VNTR followed the protocol published by (Curran et al., 2001). Genotype frequencies at all 3 loci were in Hardy-Weinberg Equilibrium ($p > 0.10$).

2.2.3 fMRI acquisition

The fMRI acquisition and preprocessing methods below are identical to a previously published study using a portion of the same individuals as the current study (Hwang, et al., 2012). Resting state data were acquired at the University of Pittsburgh Medical Center's Magnetic Resonance Research Center on a Siemens 3T Tim Trio MRI scanner (Erlangen, Germany). Participants were acclimated to the MR scanning environment for 15 minutes in a mock scanner. During the scan, each participant was asked to close his or her eyes and relax but not fall asleep. Respiration and heartbeat were recorded using a respiration belt and a pulse ox meter attached to the left index finger. Functional resting state images were acquired using an echo-planar sequence sensitive to BOLD contrast (T_2*). Parameters for the functional scan were: TR = 1.5 s, TE = 29 ms, flip angle = 70°, voxel size = 3.125 × 3.125 mm in-plane resolution, 29 contiguous 4-mm axial slices for a total scan time of 5 minutes. A magnetization-prepared rapid gradient-echo

sequence (MPRAGE) was acquired as a structural scan. Parameters for the MPRAGE were: repetition time [TR] = 1570 ms, echo time [TE] = 3.04 ms, flip angle = 8°, inversion time [TI] = 800 ms, voxel size = 0.78125 × 0.78125 × 1 mm, 200 TRs.

2.2.4 fMRI preprocessing

Resting state data were preprocessed using AFNI (Cox, 1996) and FSL (Smith et al., 2004). We used Freesurfer's automated segmentation program (Fischl et al., 2002) to segment gray matter, white matter, ventricles and non-brain tissue (NBT) from each participant's MPRAGE scan. These anatomical parcellations were used to extract signal from white matter, ventricles and NBT from the resting state fMRI scans. Preprocessing steps included: (1) removal of sudden spikes caused by MR artifacts or large head movement, (2) slice-timing correction, (3) motion correction (see below for details), (4) co-registration, (5) scaling each voxel time series to a mean value of 100, and (6) linear detrending. Next, using the ANATICOR program in AFNI (Jo, Saad, Simmons, Milbury, & Cox, 2010), we reduced hardware noise, the draining vessel effect, and motion artifacts in each grey matter voxel via regression of the following nuisance variables: (1) six-parameter motion regressors, (2) local white matter regressors averaged from white matter voxels within a spherical mask (radius = 30 mm) centered at each grey matter voxel of interest, (3) ventricle signal regressors, and (4) NBT regressors. We did not remove the global signal due to evidence suggesting the artificial introduction of anticorrelations when doing so (Saad et al., 2012). Instead, we calculated the effect of respiration and heart rate from recorded physiological parameters, using the RetroTS program in AFNI 2008(Birn, Murphy, & Bandettini, 2008; Glover, Li, & Ress, 2000) and regressed these physiological time-series from the fMRI data.

Using measures of head movement obtained from AFNI's rigid-body realignment algorithm (3dvolreg), we averaged translation and rotation values in the x, y, and z directions to calculate root mean square (RMS) of linear and angular precision. Any participant who exceeded a RMS of 1 mm (translation) or 1 degree (rotation) was excluded. There were no significant differences of head motion across age ($P = 0.15$). Further, for individuals who were included in the analyses, using the methods proposed by Power et al., (2012), we calculated frame-wise displacement (FD) and RMS variance of the temporal derivative of the time-series (DVARS). FD and DVARS values were used to identify volumes in the fMRI time series to remove from data analysis. Using the same threshold as Power et al., we removed (censored) volumes where FD exceeded 0.5 mm and DVARS exceeded 0.5 % signal change. We removed 7% of volumes in individuals under the age of 13, 2% in individuals between 13 and 17 and .2% for individuals above 18 years of age. Time series were subsequently bandpass filtered at $0.009 \text{ Hz} < f < 0.08 \text{ Hz}$ and voxels were spatially smoothed using a 5 mm full width at half maximum Gaussian kernel. Preprocessed fMRI data were spatially aligned to each participant's MPRAGE scan using FSL's nonlinear registration procedure (FLIRT and FNIRT).

2.2.5 fMRI analyses

Using Freesufer's automated subcortical segmentation program (Dale, Fischl, & Sereno, 1999), we created striatal masks for left and right NAcc, caudate and putamen in each participant's MPRAGE in native (unwarped) space (Figure 5 (top)). Using singular value decomposition in AFNI (1dsvd), we identified the first principal component vector in the time series within each striatal mask of each participant's resting state scan. We then correlated the vector with time

series in every voxel in the resting state scan. Voxel-wise correlation values were subsequently transformed into Fisher's Z-scores. Next, using Freesurfer's cortical segmentation (Fischl, Sereno, & Dale, 1999), we created masks in right and left inferior frontal gyrus (IFG), right and left middle frontal gyrus (MFG), right and left superior frontal gyrus (SFG), right and left oribital frontal cortex (OFC) and dorsal anterior cingulate cortex (dACC) (Figure 5 (bottom)). Using these masks and the six correlation maps (one for each striatal seed), we identified the top 25 percent of correlated voxels from each striatal seed to each prefrontal mask in each participant that were also contiguous in clusters of at least 5 voxels (281.25 mm^3). In this manner, we only selected prefrontal voxels that demonstrated a strong correlation with the respective striatal seeds to further explore whether connectivity strengths varied as a function of age and/or genotype. Average correlation values were extracted from these functionally defined clusters within each prefrontal mask.

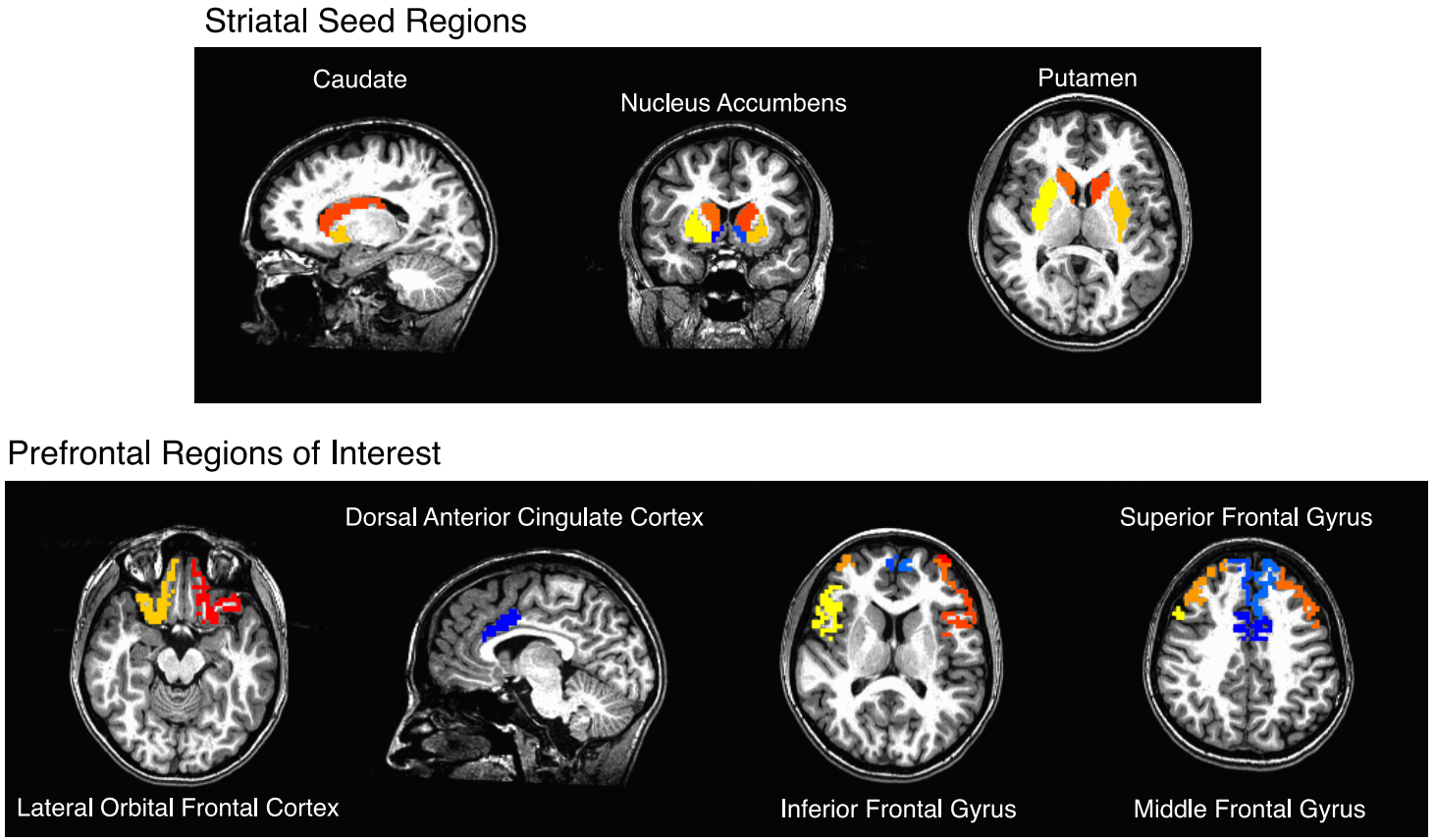

Figure 5. Graphical depiction of striatal seed regions and prefrontal ROIs on a representative participant's MPRAGE
Striatal seeds and prefrontal ROIs were segmented using FreeSurfer's subcortical (Fischl, et al., 2002) and cortical (Dale, et al., 1999) segmentation routine. In each participant's resting state data, we extracted the first component vector from each striatal region and correlated it the time series in every voxel in the brain. Next, we selected the 25% most highly correlated voxels from each striatal seed in each prefrontal ROI that also formed a contiguous cluster of at least 5 voxels.

2.2.6 Group level linear mixed effects models

We used R (an open-source statistical program; R Development Core Team, 2009) for group-level analyses. We ran several model-fit analyses to determine the best fit for the age variable. We determined the optimally fitting model across all striatal – PFC regions of interest (ROI) pairs on the basis of the Akaike Information Criterion (AIC) model fit index. The AIC index selected because of its use in other developmental studies that compared different shapes across development (Kail & Ferrer, 2007). We compared inverse, linear and quadratic age models. Therefore, the AIC was selected because it allows for comparison of models that are not nested such as the linear and inverse age models as well as allows for comparing across models that have different number of parameters such as the linear and quadratic models. Lower AIC values reflect better model fit to the data. Given evidence of additive allelic influences of the genes of interest, genotype was coded as an ordinal factor reflecting increased number of DA availability for *COMT* (met/met:2, val/met:1, val/val: 0), *MAOA* (3R/3R: 2, 3R/4R: 1, 4R/4R:0) and *DAT1* (9R/10R:0 & 10R/10R:1). Due to differences in number of participants in each genotype group, orthogonal polynomial coefficients for each factor were weighted to reflect unequal sample sizes (Gaito, 1977). The multilocus composite score was calculated similar to prior studies (Nikolova, et al., 2011; Stice, et al., 2012), with a summation of allelic load (reflecting increased DA availability) across loci for each individual. This resulted in six separate values across participants. Composite values were mean centered and entered as a continuous variable. Final mixed effects models were then run using the chosen age model separately for each genotype as well as the composite score. Sex was included as a covariate in all models and subject was included as a random factor. Outcome variables were each striatal seed to PFC ROI correlation.

We also ran regressions on volumetric data for each striatal and PFC ROI based on prior research suggesting that there is a protracted structural development of gray matter volume over adolescence (Gogtay, et al., 2004; Sowell, et al., 2002), as well as an influence of these polymorphisms on gray matter volume (Raznahan et al., 2011) (Alia-Klein, et al., 2011; Dumontheil, et al., 2011; Good et al., 2003; Honea et al., 2009; Mechelli et al., 2009; Zinkstok et al., 2006). Results were corrected using simultaneous inference tests for parametric models to correct for multiple comparisons across all striatal – PFC combinations (Hothorn, Bretz, & Westfall, 2008) in R.

2.2.7 Variance Analyses

In order to determine if genotype explained *greater* amount of variance in connectivity above the age effect (of the age model we selected based on the AIC index), we ran step-wise regressions and calculated change in R^2 for all the striatal - PFC pairs that showed a significant age effect.

2.3 RESULTS

2.3.1 Volumetric Results

AIC indices for striatal seed and prefrontal ROI volumes suggested that the linear model was the best fit over the inverse and quadratic models. There were no effects of age or genotype effects for any of the striatal volumes. There were significant effects of age in left IFG (B = -115.507, Z

= -3.673, p = 0.004, corrected), right IFG (B = -99.579, Z = -3.167, p = 0.0242), left MFG (B = -207.258, Z = -6.591, p = 0.001, corrected), right MFG (B = -180.780, Z = -5.749, p = 0.001, corrected), left SFG (B = -260.926, Z = -8.297, p = .001, corrected), right SFG (B = -182.794, Z = -5.813, p = 0.001, corrected), and left OFC (B = -95.694, Z = -5.813, p = .001, corrected). All results demonstrated a significant decelerating linear decline in age in prefrontal volumes (Figure 6).

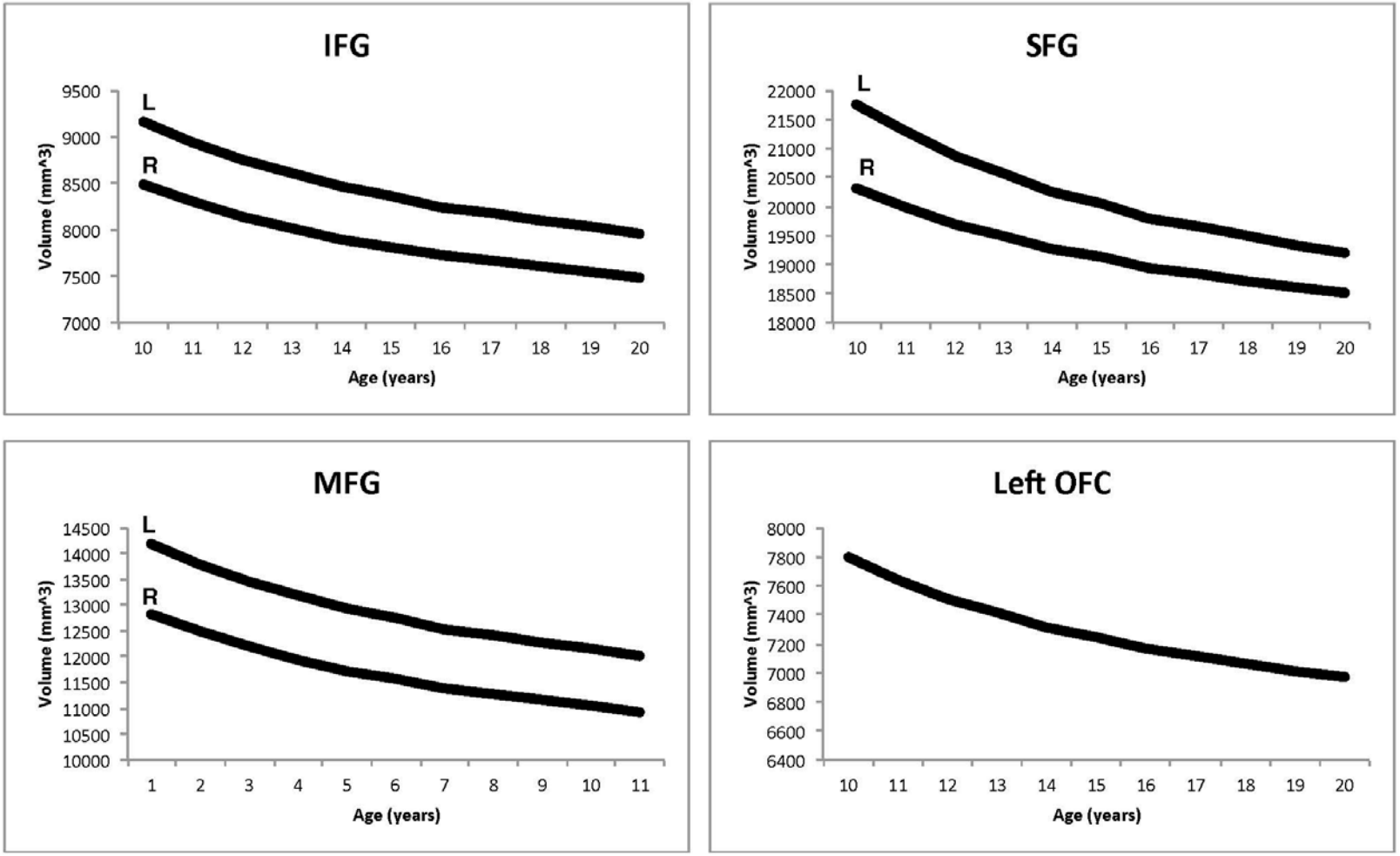

Figure 6. Volumetric results
Line graphs depicting change in gray matter volume of prefrontal structures across age. Age effects were significant at $p < .05$, corrected. L = Left, R = Right.

2.3.2 Resting State Results: Effect of Age

AIC indices for all resting state models suggested that the inverse model was the best fit over linear and quadratic. We had data for correlations with 6 seeds and 9 prefrontal ROIs totaling 54 models. There were significant effects of age^{-1} in the connectivity between left caudate and left IFG (B = 3.3163, Z = 3.361, p = 0.0231 corrected), right caudate and dACC (B = 3.2560, Z = 3.300, p = 0.0275, corrected), right caudate and left IFG (B = 4.2840, Z = 4.341, p < .01), and right caudate and right IFG (B = 3.4390, Z = 3.485, p = 0.0160, corrected). We also found trend levels for corrected significance between left caudate and dorsal ACC (B = 2.9666, Z = 3.006, p = 0.0654, corrected), left caudate and left SFG (B = 2.8514, Z = 2.890, p = .0892, corrected), right caudate and left SFG (B = 2.8878, Z = 2.926, p = .0807, corrected), and right putamen and left IFG (B = 2.8742, Z = 2.913, p = .0835, corrected). All results had positive beta values for the effect of age^{-1}, suggesting a decelerating decline in connectivity strength across age. In subsequent models, when each genotype and genotype by age^{-1} interactions were added, significant age effects on resting state connectivity did not change (except the degree of significance).

2.3.3 Resting State Results: Effect of Genotype

Separate mixed effect models including each genotype and age by genotype interaction terms were subsequently conducted. There was no main effect of *COMT* or *DAT1* genotype or age^{-1} by

COMT or *DAT1* interactions on resting state connectivity in any of the striatal-PFC correlation pairs.

There were significant main effects of *MAOA* genotype on connectivity between left putamen and dorsal ACC (B = -0.058899, Z = 3.484, p = 0.0164, corrected), a trend for corrected significance in left putamen and left IFG (B = -0.049700, Z = 2.909, p = .09, corrected, p = .003627, uncorrected), left putamen and right IFG (B = -0.0556, Z = 3.295, p = 0.0299, corrected), right putamen and dorsal ACC (B = -0.065, Z = 3.834, p < 0.0100, corrected), right putamen and left IFG (B = -0.0555, Z = 3.285, p = .0301 corrected), and right putamen and right IFG (B = -0.0684, Z = 4.047, p < .01, corrected). Resting state connectivity overall decreased as a function of increasing *MAOA* 3R alleles, suggesting increased DA availability resulted in relative decreased connectivity strength (4R > 3R/4R > 3R) (Figures 7 & 8).

There was a significant *MAOA* genotype by age^{-1} interaction in the connectivity between left caudate and dACC (B = -3.984, Z = 3.539, p = 0.0128, corrected) and right caudate and dACC (B = -4.2047, Z = 3.735, p < 0.0100, corrected) suggesting a moderated effect of *MAOA* on the caudate – dACC connectivity with age. Resting state connectivity decreased as a function of increasing DA levels (4R > 3R/4R > 3R) early in adolescence with a convergence in late adolescence/early adulthood (Figure 9). Post-hoc tests testing age effects with each *MAOA* genotype showed that only the individuals hemi or homozygoes for the 4R allele showed a decline in connectivity between left caudate and dACC (B = 7.18381, Z = 4.289, p < 0.01, corrected) and right caudate and dACC (B = 7.20247, Z = 4.301, p < 0.01, corrected). The other two groups (3R/4R and 4R) showed no developmental change (p's > .05). In order to assess if gene effects were significant early in adolescence relative to late as suggested by the direction of the overall *MAOA* by age^{-1} interaction, we conducted simple effects analyses at age end points

(10-12 and 18-20 years of age). Planned follow-up simple effects analyses revealed that *younger* individuals (aged 10-12) showed a significant effect of *MAOA* in connectivity between left caudate and dACC (B = 0.10389, t = 2.265, p = 0.0329) as well as right caudate and dACC (B = 0.11306, t = 2.444, p = 0.228), whereas older individuals (aged 18-20) did not (p's > 0.05) (Figure 9).

There were main effects of the Composite score on connectivity between left caudate and dorsal ACC (B = -0.0703, Z 3.696, p < 0.01, corrected), and a trend for corrected significance between left caudate and right IFG (B = -0.0553, Z = 2.911, p = .085). There was a significant main effect of the Composite score between left putamen and dACC (B = -0.0621, Z = 3.264, p = 0.0315, corrected), right putamen and dACC (B = -0.07081, Z = 3.724, p < .01, corrected) (Figure 2.4), right putamen and left IFG (B = -0.06039, Z = 3.176, p = 0.0413, corrected), and right putamen and right IFG (B = -0.0650, Z = 3.421, p = .0196, corrected) (Figures 7&8). Individuals with decreasing levels of DA (decreasing in composite score) showed increased connectivity for all striatal prefrontal pairs. Connectivity between right caudate and dACC, which demonstrated a significant effect of age^{-1} (see above), was further moderated by composite score as evidenced by a significant composite by age^{-1} effect (B = 4.620, Z = 3.447, p = 0.017, corrected) (Figure 9). In order to assess if gene effects were significant early in adolescence relative to late as suggested by the direction of the overall composite by age^{-1} interaction between the right caudate and dACC, we conducted simple effects analyses at age end points (10-12 and 18-20 years of age). Planned follow-up simple effects analyses revealed that *younger* individuals (aged 10-12) showed a significant effect of composite score in the connectivity between right caudate and dACC (B = 0.12782, t = 2.097, p = 0.0467) and a trend for significance between left

caudate and dACC (B = 0.11285, t = 1.870, p = 0.737). There were no gene effects among older individuals (p's > 0.05).

Due to findings that prefrontal volumes also showed a decline across age, we subsequently ran models using volume as an additional covariate. Significant results did not change, but AIC model fit indices worsened (were larger) so we report our original results, not correcting for prefrontal volumes.

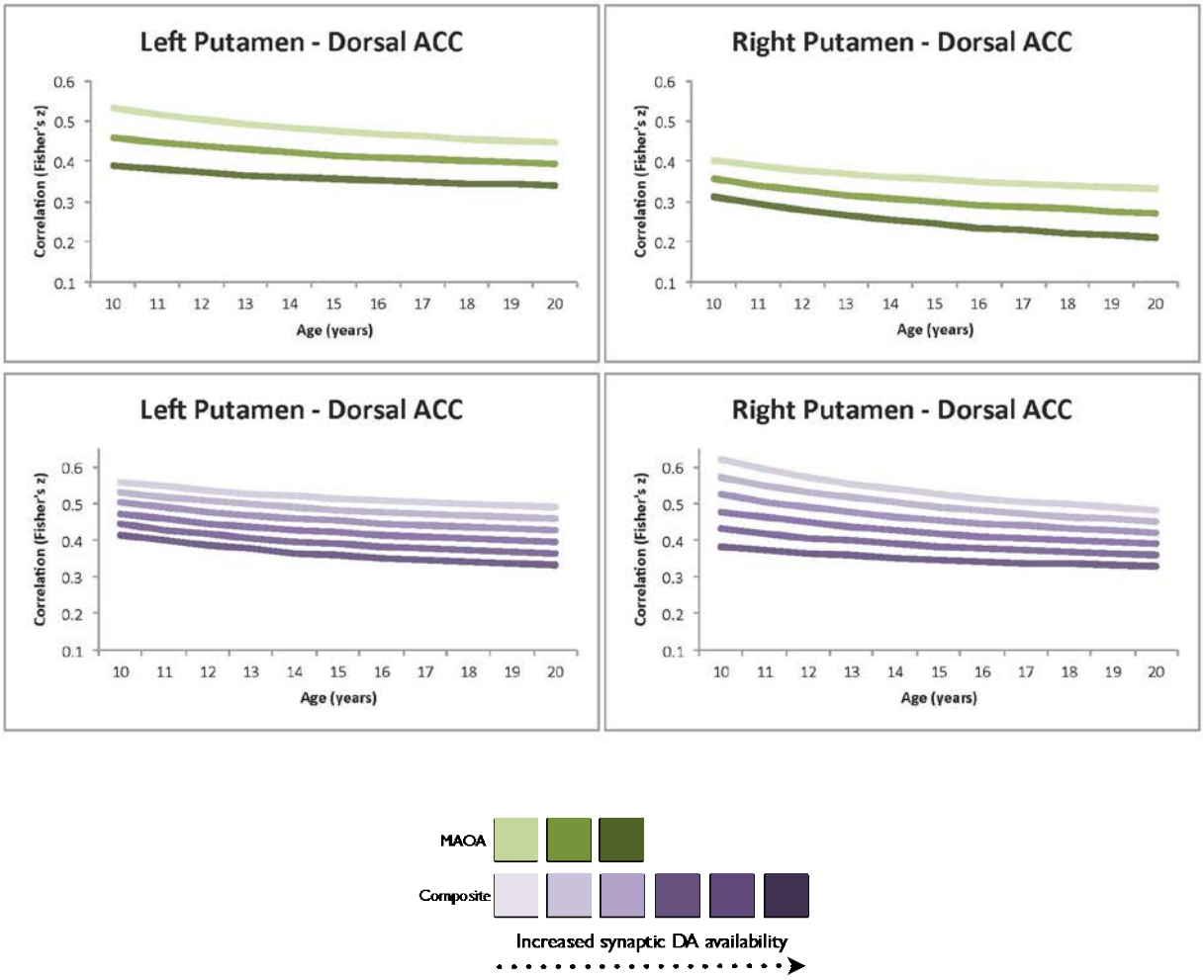

Figure 7. Regression lines for connectivity between Putamen and dACC
Graphs depicting regression lines for the connectivity between bilateral putamen and dACC as a function of age and *MAOA* genotype (green) and Composite score (purple). Results were significant for a main effect of *MAOA* genotype and Composite score with individuals with *decreasing* DA levels showing relatively increased connectivity strength (all p's < .05, corrected).

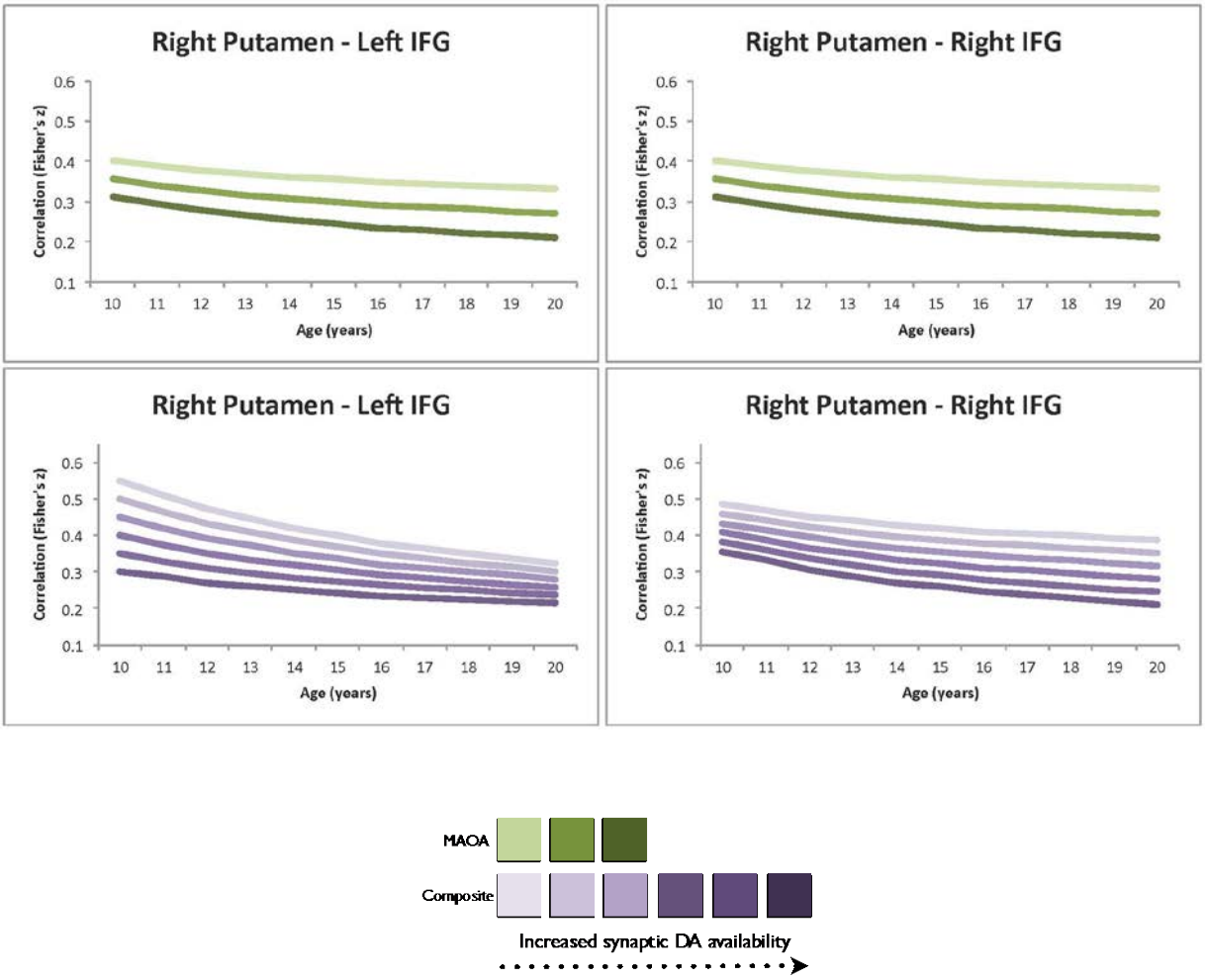

Figure 8. Regression lines for connectivity between Right Putamen and IFG
Graphs depicting regression lines for the connectivity between right putamen and IFG as a function of age and *MAOA* genotype (green) and Composite score (purple). Results were significant for a main effect of *MAOA* genotype and Composite score with individuals with *decreasing* DA levels showing relatively increased connectivity strength (all p's < .05, corrected).

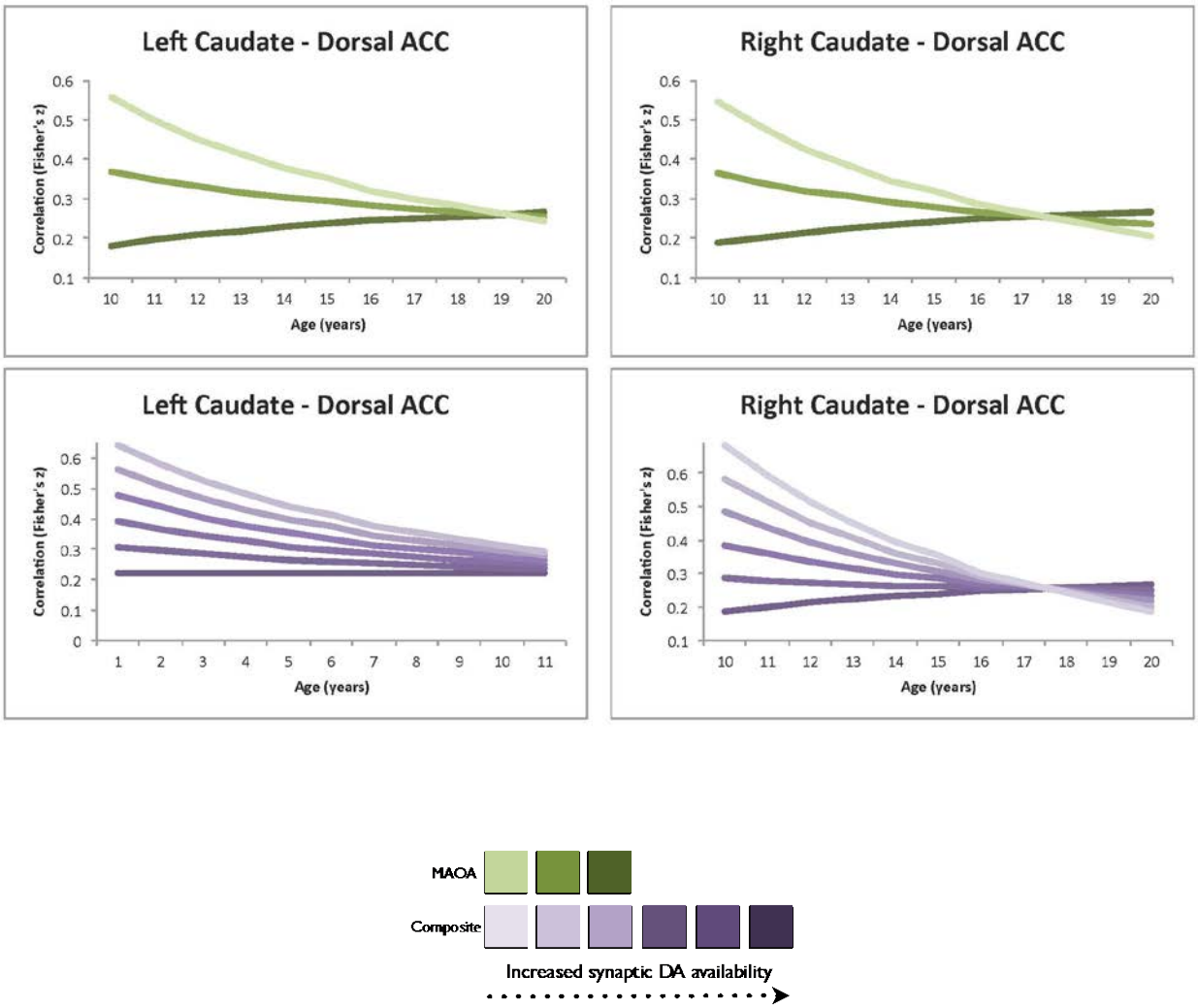

Figure 9. Regression lines for connectivity between Right Putamen and IFG
Graphs depicting regression lines for the connectivity between right putamen and IFG as a function of age and *MAOA* genotype (green) and Composite score (purple). Results were significant for a main effect of *MAOA* genotype and Composite score with individuals with *decreasing* DA levels showing relatively increased connectivity strength (all p's < .05, corrected).

2.3.4 Variance Results

Correlations between the left and right caudate and dACC showed a significant increase in variance explained above the age^{-1} effect. We found that for the Left Caudate – dACC, age^{-1} explained 3.4% of the variance of the connectivity measure. The composite score explained .46% of the variance above the age effect. In addition, the composite score explained more of the variance than each genotype alone, but *less* of the variance than a model with all genotypes included (.64% of variance above the age^{-1} model). For the Right Caudate – dACC, the age^{-1} model explained 6.2% of the variance. The Composite score explained .13% above the age^{-1} model, which was a larger proportion of the variance than each of the single genotypes. However, the model with all genotypes explained a larger proportion of the variance than the composite score (.25% of the variance above the age^{-1} model).

2.4 DISCUSSION

We examined the changes in frontostriatal connectivity across adolescence and the moderating influence of DA availability (as measured by genotype) on rsFC. It is important to note that we only selected areas that were strongly coupled with each striatal seed within each individual. Therefore, genetic and age effects reflect a change in *relative* connectivity strengths within well-established networks, rather than speaking to absence or presence of connections. We predicted that changes in rsFC as a function of DA availability would reflect a modulation of *tonic* DA signals in PFC and striatum.

Overall, results demonstrated a *decrease* in rsFC over adolescence between the caudate and dACC, IFG and SFG. Connectivity between other prefrontal and striatal regions did not change across age. In addition, we found that *MAOA* genotype and the multi-locus composite score further moderated the age-related declines in caudate-dACC connectivity, with a genotype effect early in adolescence (10 years of age) that converged into late adolescence/early adulthood (20 years of age). Importantly, we found that only individuals with the relatively *lowest* amount of DA availability (*MAOA* 4R) showed an age-related decline in connectivity, whereas individuals with relatively middle or higher levels showed no age-related change. Lastly, we found main effects of *MAOA* genotype and Composite score (but not age) in connectivity between putamen and dACC and IFG, suggesting a rank-order stability in gene effects that persisted across this developmental stage. The potential significance of these effects are discussed in more detail below.

2.4.1 Age-related declines in connectivity

During adolescence, a dramatic reorganization of brain connectivity occurs as evidenced by structural and functional research at both micro (cellular) and macro (systems) levels of functioning. As evidenced in prior studies, we demonstrate an overall *decline* in caudate – prefrontal connectivity across adolescence, perhaps indicative of a relative decreased reliance on cortical-subcortical connections in favor of cortical-cortical ones that support goal-directed behaviors (i.e. PFC to Parietal and temporal cortical areas) (N. U. Dosenbach, et al., 2010; Fair et al., 2009). Furthermore, structural connectivity findings suggest that white matter tracts that project to and from striatum, the ACC, as well as within striatum are the last to mature over development, showing continued but *decelerating* increases in white matter integrity into the third and fourth decade of life (Lebel, et al., 2008). As our sample ranged from 10 – 20, it is possible that maturation of rsFC strengths between striatum and PFC continue into the twenties, which should be explored in future studies.

There were no age-related changes between putamen and PFC rsFC over adolescence. The putamen, which is largely involved in motor functions, has been previously linked to primary motor functions, as well as cognitive (Alexander & Crutcher, 1990; Alexander, et al., 1986) with subregions of putamen showing strong connections to primary and supplementary motor cortex as well as lateral PFC (Choi, Yeo, & Buckner, 2012; Di Martino, et al., 2008; Draganski et al., 2008). Lack of developmental change with putamen could be reflective of an earlier development of *sensorimotor* function relative to cognitive functions (Chugani, et al., 1987).

2.4.2 Influence of DA availability on frontostriatal rsFC over adolescence

The strong regulatory influence of PFC on striatal circuits is grounded in the function of DA, as studies have demonstrated that activation of the PFC stimulates DA release in striatum (Strafella, Paus, Barrett, & Dagher, 2001), both directly through glutamatergic mechanisms (Taber & Fibiger, 1995) as well as through the activity of midbrain DA neurons (Karreman & Moghaddam, 1996). We found two distinct patterns of activity as a function of increasing DA availability. 1) A main effect of genotype (*MAOA* and Composite score) on putamen – IFG rsFC and 2) An age by genotype (*MAOA* and Composite score) interaction between caudate and dACC rsFC.

Connectivity between the putamen and IFG, which showed no developmental change, showed a significant effect of *MAOA* genotype and the Composite score. The putamen is involved in largely motor and cognitive functions, with *caudal* areas of the putamen strongly connected to motor and supplementary motor cortex and *rostral* areas showing connections with lateral PFC, specifically IFG and insula (Di Martino, et al., 2008; Postuma & Dagher, 2006).

Given that rsFC is a measure of *slow* fluctuations in the BOLD signal, *tonic* DA activation, which operates in a time-scale of seconds, may play a larger role in the modulation of the signal. The role of tonic DA in the brain is primarily to guide goal-directed behavior, with prefrontal tonic DA playing a regulatory role in optimal PFC signaling and regulation of striatal function (Bilder, et al., 2004). Tonic DA stimulation in the PFC follows an inverted-U shaped dose-response curve (Vijayraghavan, et al., 2007), and may be modulated by genetically-mediated variability in prefrontal DA availability (Bilder, et al., 2004). Although *COMT* is the predominant DA degredation enzyme in PFC, it plays a significantly smaller role in striatal DA clearance similarly, *DAT1,* which is predominant in the striatum has smaller influence on the

PFC (Sesack, Hawrylak, Matus, Guido, & Levey, 1998). We did not observe any connectivity differences as a function of *COMT* or *DAT1* genotype. Differences in overall tonic DA availability, (as measured by the *MAOA* genotype and the Composite score) rather than increased influence in specific regions (i.e *COMT*-PFC, *DAT1* – striatum) might play a stronger role in modulating connectivity patterns. Our findings that increased DA availability in the whole brain resulted in decreased rsFC between caudate and dACC and IFG as well as putamen and IFG was counter to our predictions that increased DA would increase connectivity, especially with lateral PFC, as suggested by prior studies in adults (C. Kelly, et al., 2009; Nagano-Saito et al., 2008). However, those studies examined pharmacological manipulations of DA levels to look at *within* subject changes in connectivity, rather than the influence of baseline differences in DA availability between subjects, which may be one reason for such differences. Furthermore, *tonic* DA release from the VTA is thought to attenuate inputs to the PFC (Goto & Grace, 2005). Although the current study wasn't examining the effect of tonic release in the VTA, it is possible that genetically mediated increases in tonic DA neurotransmission reduce subcortical inputs to PFC, thereby reducing functional coherence, but only in individuals with relatively decreased DA availability.

In the current study, it is difficult to discern the mechanism of action of increased DA availability on specific DA receptor activation as we did include measures of receptor density or function. However, as inhibitory D_2 and D_2 autoreceptors are more abundant in the caudate and putamen, and excitatory D_1 receptors in the PFC (Camps, et al., 1989), increases in overall DA availability may increase excitatory activity in PFC, while increasing D_2 receptor activation in striatum relative to the three loci of interest. Furthermore, D_2 receptor function in PFC is thought to come online later (late adolescence-early adulthood) than D_1 receptor function (Tseng &

O'Donnell, 2007), reflecting sudden shift in the influence of local interneuron function in the PFC, which can alter low-frequency fluctuations in signaling in early adulthood. Although future work is needed to assess the direct significance of a later maturing aspect of the PFC, these differences may help account for changes in early adulthood that necessitate extending the age window to observe a more complete pattern of change. Although changes in DA function are not directly associated with oscillatory fluctuations in BOLD response, they may play a role in altering the relative coupling between PFC and striatum. Given limitations of human neuroimaging methodologies on the precision of gene effects on the DA system and on the neuronal dynamics of functional coherence (as well as the functional significance of both), future work incorporating animal models may be necessary to answer these questions.

Surprisingly, we did not observe age or genotype related differences in connectivity with the NAcc. The NAcc has been of particular interest in adolescence due to its central role in reward processing, motivated behaviors, and sensation seeking. We did not find any quadratic patterns of connectivity over adolescence with the NAcc despite prior evidence suggesting hyperactivity in the NAcc in adolescence relative to childhood or adulthood, and increased connectivity between NAcc and ventromedial areas of the PFC during rewarded decision-making (Christakou, et al., 2011; Somerville, et al., 2010) between adolescence and adulthood. However, most previous research has focused on discrete age groups rather than considering age as a continuous variable and prior research has also focused on task-based connectivity and not resting state. Although research suggests that task-based connectivity is correlated with rsFC (Biswal, et al., 1995), it is possible that certain networks that show increased connectivity during task, do not show the same effects during rest.

The pattern of connectivity between the caudate and dACC followed one of our predicted patterns (Figure 3.4), with gene effects on caudate-dACC connectivity were evident in early adolescence, converging into late adolescence/early adulthood. Furthermore, individuals with the lowest levels of DA availability guided the overall decrease in connectivity with age. Individuals with *relatively decreased* DA availability may undergo more dramatic development change in network-level connectivity, which may confer an increased vulnerability in these individuals relative to individuals with higher levels of DA through adolescence.

These findings are in line with our hypothesis that the relative influence of DA availability changes across adolescence as the DA system itself undergoes reorganization. Animal research suggests that DA concentrations peak in adolescence declining into adulthood (Badanich, et al., 2006; Philpot, et al., 2009), concurrent with a decline in DA autoreceptor function into adolescence, which can lead to an increase in synaptic DA availability (Andersen, Dumont, & Teicher, 1997). Furthermore, there's an earlier (preadolescent) peak in both D_1 and D_2 densities in striatum with steady declines thereafter (Lidow & Rakic, 1992; Seeman, et al., 1987). The most consistent evidence for transporter function is that in subcortical regions, transporter density increases into late childhood followed by a plateau (Coulter, et al., 1996; Tarazi, et al., 1998). Given the restructuring and eventual stabilization of the DA system (O'Donnell, 2010), particularly during the transition from childhood into adolescence, one might expect that genetically-driven variability in DA functioning might be distinct in adolescence relative to adulthood, and in a typically developing population, gene effects on brain function may diminish as brain networks reach stability into adulthood. For example, studies have demonstrated more diffuse rsFC earlier in development in the ACC relative to adulthood that may reflect changes in synaptic pruning (A. M. Kelly et al., 2009), suggestive of an increase in

functional specificity in PFC, although these were in more *ventral* areas of the ACC rather than dorsal. Although our results do not speak to diffuse or focal patterns of activation (or coherence) specifically, we found that overall the influence of DA availability on caudate-dACC connectivity decreased over adolescence, converging into early adulthood, perhaps reflecting stability into adulthood that is less perturbed by relative differences in neurotransmitter function.

Furthermore, studies suggest that the dorsal striatum (including caudate and putamen) undergoes a more dramatic change in receptor expression (notably peaks in D_1, D_2, and D_4) relative to the NAcc where findings are more mixed (Seeman, et al., 1987; Tarazi & Baldessarini, 2000; Teicher, et al., 1995). To this end, perhaps the relative influence of DA availability over adolescence is larger in dorsal striatal structures than the NAcc due to a more protracted development of receptor expression. The greatest developmental change in connectivity patterns was between cognitive circuits (caudate to dorsal ACC) relative to primarily affective or motor related circuits, which is in line with previously discussed models of adolescent behavior (Casey, et al., 2008), suggesting an increased protracted development of regions subserving cognitive control over adolescence. The dorsal striatum, which is central for incentive-based learning (e.g. integrating reward information with behavior) and cognitive control (Ashby, Turner, & Horvitz, 2010; Pasupathy & Miller, 2005) as well as integrating reward and the dorsal ACC, which is essential for error monitoring and updating of behaviors (Botvinick, Nystrom, Fissell, Carter, & Cohen, 1999; Velanova, et al., 2008) may together play a role in cognitive flexibility, updating, and responding based on outcomes.

Overall, we show that frontostriatal circuits are generally established by adolescence, consistent with prior research suggesting that frontostriatal connections are established relatively early with respect to other longer-range connections across the cortex (Fair, et al., 2009;

Goldman-Rakic, 1987), but some changes persist, specifically circuits that subserve cognitive behaviors. Furthermore, we found that DA availability as measured by polymorphisms in DA genes that influence synaptic clearance of DA moderate age effects in cognitive circuits, while showing no influence on others.

2.4.3 Limitations

Future studies should expand the age range to encompass a wider developmental window to examine network connectivity beyond adolescence as white matter tracts between subcortical and cortical circuits continue to develop. Animal models and more direct examinations of DA signaling on the brain should be incorporated with imaging genetics techniques to speak more to specific mechanisms driving age related differences. Lastly, sample sizes should be larger in order to examine the influence of many genes and look at epistatic and interactive effects in addition to additive.

3.0 INFLUENCE OF SYNAPTIC DA AVAILABILITY ON FRONTOSTRIATAL BRAIN FUNCTION UNDERLYING THE INFLUENCE OF INCENTIVES ON INHIBITORY CONTROL IN ADOLESCENCE

3.1 INTRODUCTION

Goal-directed incentive-driven behaviors involve maintaining a representation of the values (positive and negative) of all options in order to make an optimal decision within the current context. Animal and human evidence suggests that frontostriatal brain function involved in motivated behaviors demonstrates a protracted development over adolescence, both structurally and functionally. Collectively these studies have demonstrated that adolescents recruit similar brain regions to support cognitive and motivational processing as adults. What differs is the extent to which these regions are utilized for various tasks. More recently, emphasis has been placed on examining how incentives influence behavior to better understand how reward and control systems interact.

Functional neuroimaging studies have demonstrated differential recruitment of reward processing regions by adolescents relative to adults and children following a non-linear pattern over age (Bjork, et al., 2010; Ernst, et al., 2005; Galvan, et al., 2006; Geier, et al., 2010; May et al., 2004; Van Leijenhorst, et al., 2009). For example, Galvan et al. (2006) demonstrated that adolescents show increased recruitment of ventral striatum and decreased activity of orbital

frontal cortex relative to adults and children when receiving a reward. Importantly, this and other studies have demonstrated that cortical regions involved in more executive aspects of reward processing (i.e. the OFC), showed a linear development from childhood to adulthood whereas ventral striatum, a region associated with reward anticipation and in reward-related behaviors peaked in activity in adolescence (Durston et al., 2006; Geier, et al., 2010; van Leijenhorst, et al., 2010; Van Leijenhorst, et al., 2009). Geier et al. (2010) demonstrated that adolescents engage ventral striatum later in a reward trial than adults, but do so in an exaggeration fashion during reward anticipation. Conversely, Bjork et al. (2004) demonstrated that adolescents engage the ventral striatum less during reward anticipation relative to adults. These discrepant findings may be related to task-specific differences, but overall demonstrate differences in engagement of the reward system in adolescence.

Importantly, studies have shown that rewards enhance cognitive control behaviors and enhance activity in brain regions that are associated with cognitive control (Geier, et al., 2010; Padmanabhan, Geier, Ordaz, Teslovich, & Luna, 2011). We recently published findings showing that not only do reward incentives improve inhibitory control, but also demonstrate a differentiation in dorsal and ventral striatum in adolescents and in OFC in adults. Importantly, increased vs activity in adolescents is seen during the preparatory period immediately previous to the response in comparison to adults who show this effect immediately after reward cue presentation. These findings suggest that 1) behaviors that are difficult for adolescents, such as cognitive control, are enhanced by reward incentives, 2) performance is improved by the concurrent increase inactivity of cognitive control circuitry and 3) ventral striatal reactivity occurs close to behavioral response, which may speak to impulsive decision-making.

Studies have also shown that incentives influence risky decision-making and this is coupled with engagement of ventral striatum. For example, elevated ventral striatal activity has been associated with increases in risky choices in adults, whereas increases in prefrontal activity are associated with increased risk aversion (Christopoulos, Tobler, Bossaerts, Dolan, & Schultz, 2009). This suggests a mechanism by which elevated ventral striatal activity during reward anticipation in adolescence may lead to higher chances of choosing riskier albeit more rewarding outcomes. Supporting this notion, van Leijenhorst et al., (2010) demonstrated that ventral striatal signaling in adolescence was positively related with reported risk taking. In addition, Somerville et al. (2010) found that adolescents elevated ventral striatal activity to appetitive cues were coupled with increased errors in suppression of an approach response. These findings suggest that incentives play an important role in mediating behavior and that adolescence may be especially sensitive to the influence of incentives due to heightened responses in the ventral striatum as well as relatively diminished or immature responses in the PFC.

Lastly, as described in Chapter 1, the DA system is thought to be crucial in modulating brain systems that processes incentives and resulting behaviors. Prior research has identified the NAcc and OFC are core regions in processing incentive information (Schultz, et al., 2000), and the dorsal striatum, lateral PFC and dACC in the cognitive control of behavior (Niendam et al., 2012). Furthermore, research has identified that polymorphisms in DA genes modulate the function of these systems (Aarts, et al., 2010; Bertolino, et al., 2008; Bertolino, et al., 2009; Bertolino, Rubino, et al., 2006; Bertolino et al., 2010; Blasi et al., 2005; Bosia et al., 2007; Cornish, et al., 2005; Dreher, et al., 2009; Garcia-Garcia, et al., 2010; Meyer-Lindenberg, et al., 2006; Nikolova, et al., 2011; Prata et al., 2009; Stice, et al., 2012; Yacubian, et al., 2007).

In the current study we sought to examine the influence of incentives (reward and punishment) on cognitive control of behavior using an established inhibitory control paradigm (the antisaccade task) over adolescence. We use the term valence to distinguish between the different types of incentives (Reward, Neutral and Loss). Furthermore, we sought to examine the influence of DA availability as measured with DA clearance genes (as in Chapter 2) and a multilocus composite score. As described in Chapter 1, The *COMT* val158met polymorphism (rs4680) in the third exon of the *COMT* gene, which is associated with changes in enzymatic degredation of extracellular DA primarily in the PFC (Chen, et al., 2004), has been widely studied in the context of frontostriatal circuitry (Bilder, et al., 2004), and has demonstrated an effect on brain signaling across age groups (e.g. (Dumontheil, et al., 2011)). The *MAOA u*-VNTR has been predominately associated with affective-related brain processing, having a functional influence on monoamine (including DA) degradation all over the brain (Sabol, et al., 1998). Finally, the *DAT1* VNTR, in the 3' untranslated region of the DAT gene (SLC6A3), which influences DA reuptake predominantly in striatum has been associated with changes in striatal signaling (e.g. (VanNess, et al., 2005). Lastly, using the methods of Nikolova et al., (2011), we combined the allelic variation in each of these genes within each individual, to create a multilocus composite score to explore a cumulative effect of these loci on frontostriatal connectivity over adolescence. We did not examine the role of DA receptor genes in the current study because less is currently known about the specific functional significance at the protein level of receptor gene polymorphisms relative to the three loci we chose. In addition, we wanted to restrict our analyses to genes that coded for extracellular DA clearance proteins rather than combine both clearance and receptor genes which may have differing effects on the DA system and on brain function as a whole, making findings more difficult to interpret. Finally, our sample

size limited us to choosing fewer loci, which made choosing functionally relevant and highly studied candidate genes of particular importance.

Similar to our study in Chapter 2, we predicted that different patterns of age by genotype effects could be seen across different brain areas. Notably, we predicted that in striatal reward regions, specifically the NAcc, we would see a quadratic developmental trajectory that was moderated by genotype (Figure 10.1). We predicted that the composite score would show a stronger effect in moderating age effects than individual genotypes. We predicted that executive control regions such as the OFC and lateral PFC would show a linear development across age that was also moderated by genotype (Figure 10.3). We predicted that motor control regions such as the preSMA would show no age effects, but perhaps a rank-order stability by genotype similar to our connectivity findings with Putamen in Chapter 2 (Figure 10.2). Lastly, we predicted genetically-modulated activity in some areas (i.e. dACC) may also converge over adolescence as DA modulation of key circuits become more stable into adulthood (Figure 10.4).

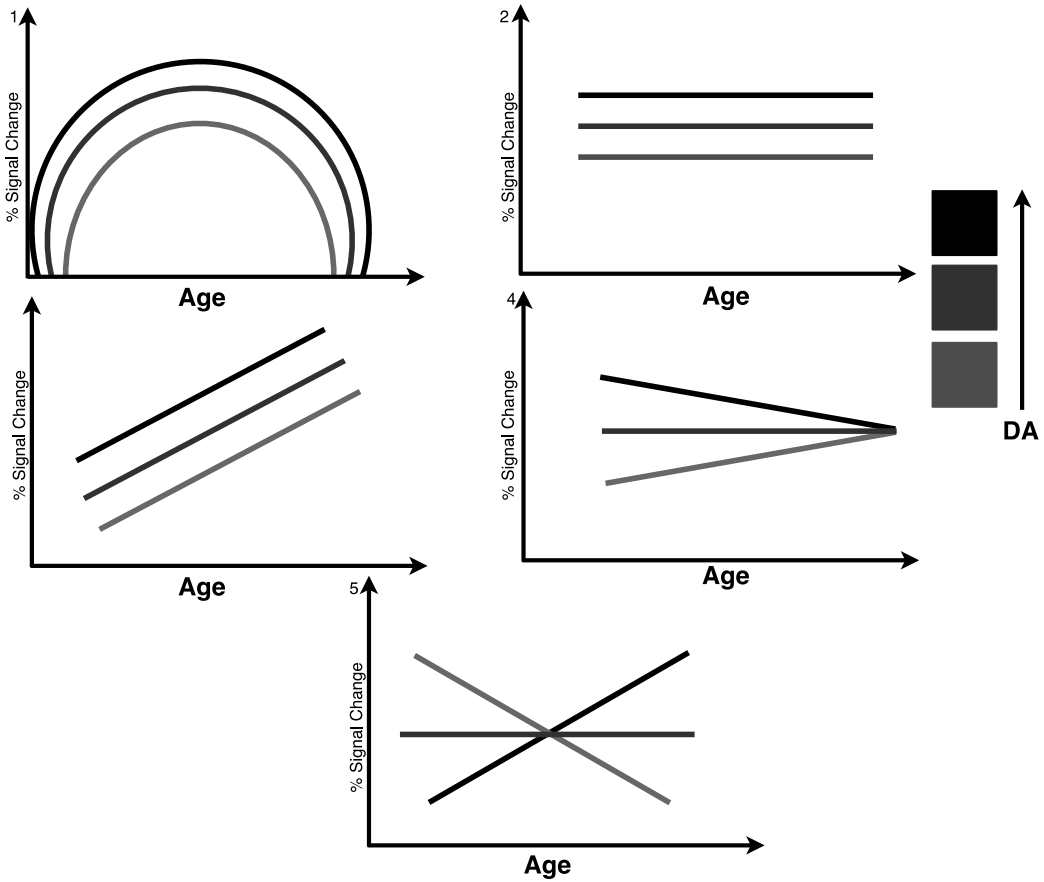

Figure 10. Predicted patterns of age by genotype effects on brain function.
On the x-axis is age and y-axis is brain function. Darker lines signify *increased* DA availability relative to lighter gray lines. DA = Dopamine

3.2 METHODS

3.2.1 Participants

A total of 167 participants between the ages of 10 and 20 were recruited as part of a first visit from a parent longitudinal study. Of the 167 participants, 124 participants were included in the fMRI analyses (Table 3.1). Figure 11 shows the genotype distributions in two-three year age bins. We excluded participants due to 1) inability to scan due to claustrophobia, 2) too much head motion, 3) bad performance or non compliance on the task, and 4) not being of Caucasian descent to eliminate potential population stratification effects. All participants had (corrected or uncorrected) visual acuity of at least 20/40 and no medical history of psychiatric neurological disease or injury and no first degree relative with a psychiatric illness as determined by interview. 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. Participants were compensated for participation in the study in addition to earnings during the fMRI reward paradigm (described below).

Table 2. Breakdown of participants by genotype

Gene		N 111	% females	Mean Age 10-20	WASI 2
COMT	Met/Met	26	38	15.17(2.97)	112.92(8.29)
	Val/Met	63	51	14.77(2.96)	107.84(11.26)
	Val/Val	35	51	16.06(2.67)	110.35(11.85)
MAOA	3R	34	53	15.52(2.84)	111.29(11.38)
	3R/4R	33	100	16.03(2.86)	110.25(9.77)
	4R	57	58	14.58(2.89)	108.25(11.10)
DAT1	9R	64	45	14.95(2.98)	108.48(11.18)
	10R/10R	60	52	15.52(2.84)	110.83(10.43)
Multilocus	3.0	16	38	15.11(2.70)	108.69(10.01)
Composite	2.5	20	40	15.24(3.00)	110.65(11.30)
	2.0	37	51	14.94(2.68)	109.22(11.04)
	1.5	28	46	15.49(3.18)	111.46(9.78)
	1.0	16	62	15.51(3.27)	109.14(12.48)
	0.5	8	50	15.28(2.32)	105.00(10.07)

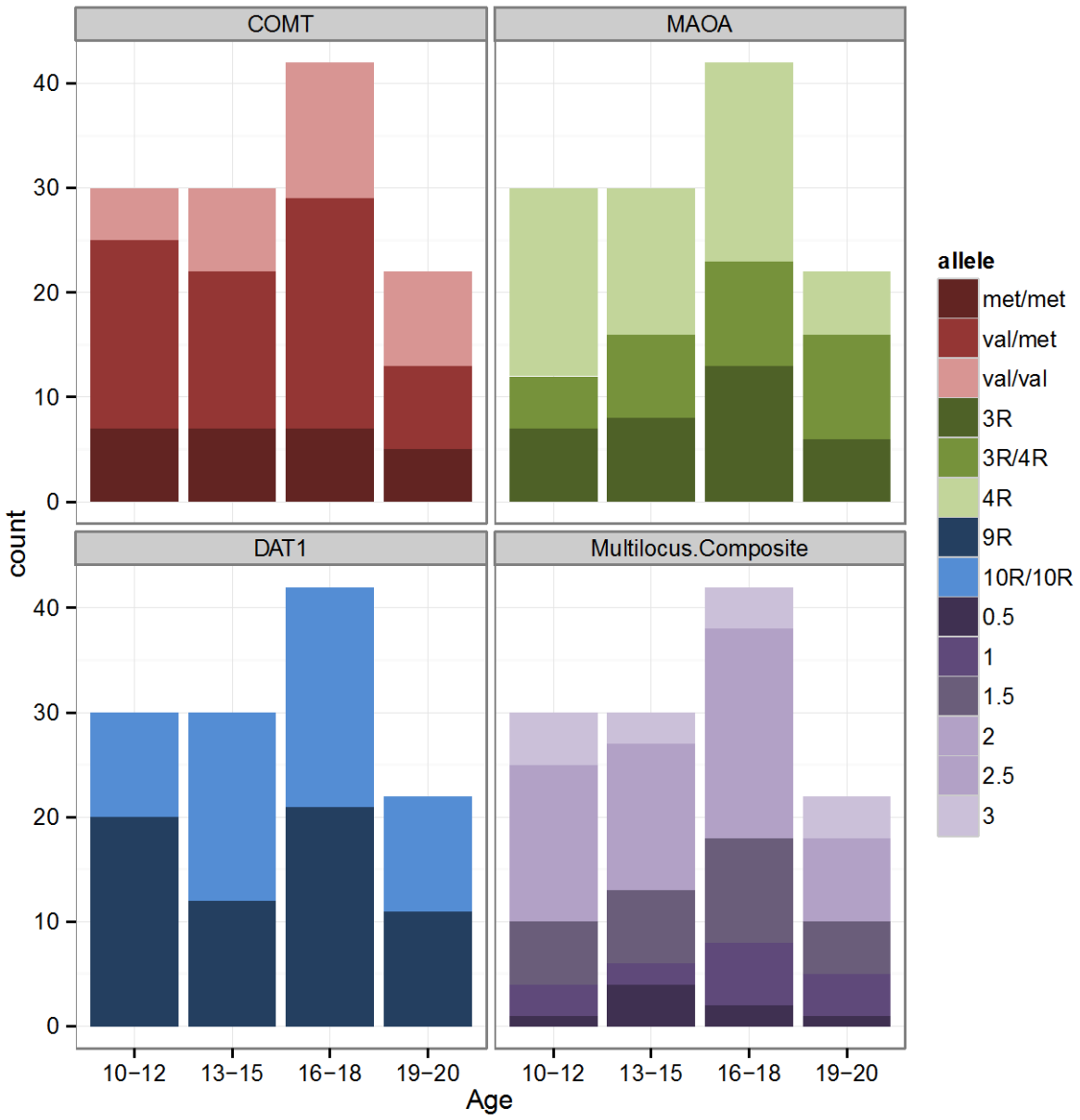

Figure 11. Genotype distributions across age

3.2.2 Pre-scan Assessments

All scan participants completed the Zuckerman sensation seeking scale questionnaire, which included subscales that measured Thrill and Adventure Seeking, Experience Seeking, Boredom, and Disinhibition (Zuckerman, 2007). Participants were also tested on the Wechsler Abbreviated Scale of Intelligence to screen for verbal, non-verbal and cognitive ability (WASI-2 part). Furthermore, in order to equate subjective reward or motivation across participants, each participant completed a brief questionnaire to choose one of several potential "rewards" that they would receive at the end of the task, depending on performance (Geier & Luna, 2011). These options included either a pre-paid $25 debit card or a gift card to various businesses in the area. Participants were also asked to rate using a Likert scale (1 - extremely valuable, 10 - not at all valuable), how valuable they thought their chosen reward is, and to write down one item that they might purchase with it. Participants were told that they could win or lose "points" during the task, which would be tallied at the end to determine the amount of reward (up to $25). They were additionally told that there would be no debt as they were starting with 100 points at the very beginning. Participants were given the number total possible points they could earn or the conversion scale of points to money in order to prevent them from keeping a running tally during the scan. The following scale was used to convert points to money at the end of the task: 0-70 points (US $10), 71-140 (US $15), 141-210 (US $20), 211-280, (US $25.00 or the chosen gift card).

3.2.3 Genotyping

High molecular weight DNA was isolated and extracted from saliva obtained using the DNA Genotek Oragene kits (DNA Genotek: Kanata, Canada). Using allele specific primers, samples were genotyped for the *COMT* val158met polymorphism (rs 4680) gene using polymerase chain reaction (PCR) following a previously published protocol (Kunugi, et al., 1997). Genotyping of the *MAOA u*-VNTR was also done using PCR, following the protocol published by (Sabol, et al., 1998). Genotyping for the *DAT1* 3' VNTR followed the protocol published by (Curran, et al., 2001). Genotype frequencies at all 3 loci were in Hardy-Weinberg Equilibrium ($p > 0.10$).

3.2.4 Eye-tracking

Eye-movements during the fMRI task were obtained using a long-range optics eye-tracking system (Model 504LRO; Applied Science Laboratories, Bedford, MA, USA). Eye position was recorded using pupil-corneal reflection from a mirror that was mounted on the head coil in the MRI scanner at a resolution of 0.5 degrees visual angle. In addition, we had simultaneous video monitoring in order to insure that participants were engaging in the task during the scan. At the beginning of the session and when necessary, between runs, a nine-point calibration of the eye was performed. Eye data were scored off-line using ILAB software (Gitelman, 2002) and an in-house scoring suite written in MATLAB (MathWorks, Inc.).

3.2.5 Rewarded ‘Bars’ Antisaccade Task

All stimuli for the task were presented using E-Prime (Psychology Software Tools, Inc., Pittsburgh, PA), and projected onto a flat screen positioned behind the MRI scanner. Participants were able to view the screen through a mirror that was mounted on a standard radiofrequency (RF) head coil. At the start of each antisaccade (AS) trial, participants saw one of three cues for 1.5 seconds (Figure 12). Cues appeared either above a white fixation cross (Reward trials: Green bars), below the fixation cross (Loss trials: Red bars), or above and below the fixation cross (Neutral trials: Gray bars). Participants were instructed that the cues indicated potential earning of points (Reward trials), losing of points (Loss trials) or no points at stake (Neutral trials). Subsequently, the fixation cross transformed from white to red for 1.5 seconds during which the participants were instructed to maintain fixation on the center cross. Next a yellow dot appeared in an unpredictable horizontal location (3, 6, or 9 degrees visual angle on either side) for 75 ms and participants were instructed to suppress a saccade to the dot and instead generate an eye movement to its mirror location. Eye-movement data were scored online during the response using E-Prime (Psychology Software Tools, Inc., Pittsburgh, PA). An auditory tone of 1163Hz peak frequency; ‘D’) would play for 400msec indicating an incorrect response, if the participant either looked at the stimulus (prosaccade error) or did not generate any eye-movement anytime during the first 1000msec after target onset.

During the task, subjects were presented with one of three incentive cues (1.5 sec) displayed at the start of each AS trial. Five green bars above a central fixation indicated to the subject that points could be earned if the trial was corrected performed. Five red bars below the fixation indicated to the subject that points could be lost if an error was generated. 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 ms) at an unpredictable horizontal location (± 3, 6, and 9 degrees visual angle). Participants 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 participants responded correctly (looked at the mirror location) a sound of a cash register would play for 400 ms (1517Hz peak frequency, `F-sharp`). Auditory tones were modified using Audacity, an open-source sound editing program (http://audacity.sourceforge.net).

The task involved the use of "catch" trials in order to separately estimate the hemodynamic response of cue, anticipation and outcome epochs of the task. 30% of the trials were catch-trials randomly interspersed throughout the task with jittered inter-trial-intervals, as described in Geier et al.,(2010) . In sum, there were 14 complete reward trials (with 6 catch trials), 14 complete neutral trials (6 catch trials), and 14 complete loss trials (6 catch trials) per run. Each run lasted 7 minutes 33 seconds. Four runs (trials randomly ordered per run) were presented per session to each participant.

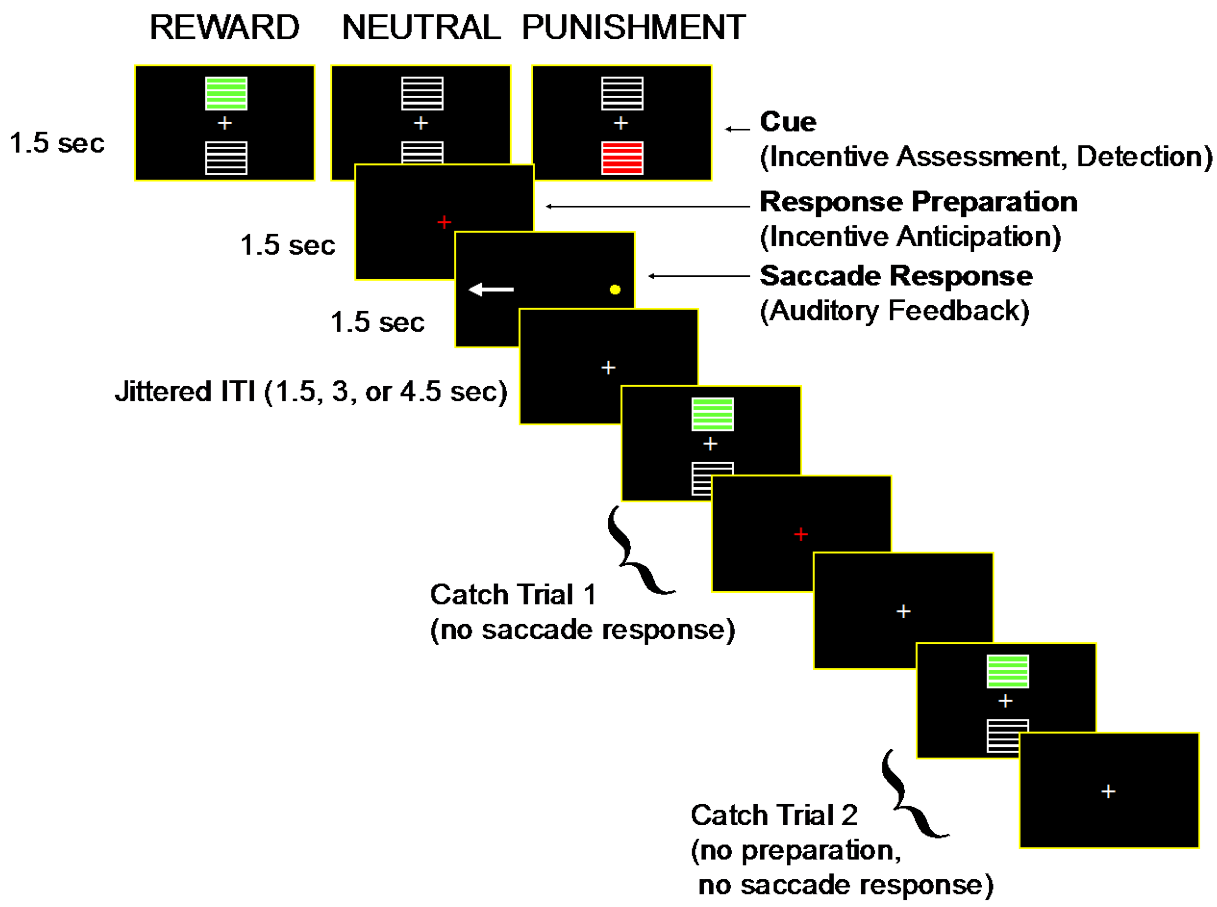

Figure 12. Graphical depiction of "Bars" Rewarded AS Task
At the start of each trial, participants saw a cue for 1.5 seconds (5 Green bars above the fixation cross, All gray bars or Red bars below the fixation cross) that let them know if the upcoming trial was a rewarded, neutral or loss trial. Next, a red fixation cross appeared to alert them to wait for the upcoming target. After 1.5 seconds, the fixation cross disappeared and a target appeared in their visual field on the horizontal plane. Participants were to inhibit the urge to look at the stimulus, and generate a saccade to the mirror location. Auditory feedback let them know if they made a correct or incorrect saccade. In 30% of the trials, either no target appeared (trial concluded after cue and preparatory phases) or no red fixation or target appeared (trial concluded after cue phase).

3.2.6 fMRI Image Acquisition and Preprocessing

Imaging data were collected using a 3.0 Tesla Trio (Siemens) scanner at the Magnetic Resonance Research Center (MRRC), Presbyterian University Hospital, Pittsburgh, PA. For the functional data, a gradient-echo echo-planar imaging sequence sensitive to blood-oxygen-dependent (BOLD) contrast (T2*) was collected (Kwong et al., 1992; Ogawa et al., 1992) was used. Data were acquired sequentially in the axial plane. 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. A three-dimensional volume magnetization prepared rapid acquisition gradient echo (MPRAGE) pulse sequence with 192 slices (1 mm slice thickness) was acquired in the sagittal plane and used as structural scans. MPRAGE images were affine registered to the Montreal Neurological Institute Template (Evans, 1993) and transformed to the MNI template space using the FNIRT program in FSL (Andersson, 2007). Warp coefficients for the nonlinear transform were calculated and stored. Functional images were preprocessed using FMRIB Software Library (FSL) (Smith et al., 2004). Images were corrected for rotational and translational head motion by aligning each volume in the time series to the volume in the middle of the 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. Slice timing correction was performed to adjust for sequential slice acquisition. For each participant, translational and rotational movements were averaged across images and used to calculate total root mean square (RMS) movement measures. Participants who moved more than 1 mm (translational) or 1 degree (rotational) were excluded from additional analyses. 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. Images were warped to the MNI template space using FNIRT and the warp coefficients from the MPRAGE warping step. Finally, signal intensity for each run was scaled to a global median of one-thousand and multiple runs were concatenated.

3.2.7 Scoring of Eye Data

Eye data were scored off-line using ILAB software (Gitelman, 2002) and an in-house scoring suite written in MATLAB (MathWorks, Inc.). Raters identified saccades using a velocity algorithm (20 deg/s) and corrected for blink artifacts and failures of the software to identify saccades. Each trial was scored for performance accuracy and latency. Trials that were unscorable due to blinks or no signal were marked as drops. Outcome variables of interest were correct AS latencies and AS response rate (number of correct trials/total number of scorable trials) for the three incentive conditions (reward, neutral, and loss). A correct response was defined as a trial when the participant did not look at peripheral stimulus when it appeared, but instead made a saccade to its mirror location. Trials were scored as errors (prosaccade errors) when participants made a saccade to the peripheral stimulus and subsequently to the correct mirror location, suggesting that participants understood the instructions of the task, but were unable to inhibit the prepotent response. We defined express saccades as a saccade latency of less than 67 ms, suggesting that participants began moving their eyes before target onset in anticipation of the target, and dropped those trials.

3.2.8 fMRI Single Subject Analysis

We ran first level statistical analyses for each participant using the general linear model in each voxel to estimate magnitude of the hemodynamic response using a canonical gamma function using AFNI's 3dDeconvolve and 3dREMLfit programs (Cox, 1996). We generated regressors for whole correct trials as well as all catch trials in each incentive condition (Reward, Neutral, Loss) within each epoch of the task (Cue, Prep, Saccade) resulting in 9 regressors. We also generated regressors for whole error trials for each incentive condition (Reward, Neutral, Loss). In addition we calculated pair-wise contrasts between incentive conditions within epochs (e.g. Reward Cue NAcc. Neutral Cue, Reward Prep NAcc. Neutral Prep, etc…) resulting in 9 contrasts. We also included baseline signal drift and six motion regressors representing motion parameters (three translational in the x, y, and z directions and three rotational) as regressors of no interest. We then calculated weighted beta estimates from the resulting maps by dividing the beta estimates by the t-statistic in each voxel. In this manner, we were able to increase reliability of the beta estimates at each voxel for each individual.

3.2.9 fMRI Linear Mixed Effects Models

Our analyses focused on *apriori* regions of interest (ROIs) that are associated with reward processing, inhibitory control and the AS task in particular. Specifically we identified regions in the bilateral FEF, SEF, bilateral MFG, bilateral IFG, dACC, bilateral OFC, bilateral NACC, bilateral putamen, and bilateral caudate. Peak coordinates of these ROIs were identified using the Neurosynth database (www.Neurosynth.org, (Yarkoni, Poldrack, Nichols, Van Essen, & Wager,

2011)). In order to minimize multiple comparisons and keep our analyses to frontostriatal circuitry, we did not include cortical eye-field areas in our analyses (such as the Frontal, Supplementary and Parietal eye fields).

The Neurosynth database is a meta-analysis of the literature, generating statistical term z-maps of the brain for specific search terms. We searched for terms that related to our brain regions of interest and selected the maps that showed overlap across the largest set of studies. We selected reverse inference maps for each term, which returned a probability in each voxel *given* observed activation at that voxel and produced a z-score depicting the statistical likelihood of that voxel being associated with that term across the hundreds of studies in the Neurosynth database that used that term. Using peak voxels from these resulting statistical maps, we generated 10 mm radius spheres for the cortical ROIs, with the exception of the preSMA for which we used a 7 mm radius sphere and the right and left MFG, which we used 12 mm spheres. For the striatal ROIs, we drew 8mm spheres for the left and right caudate and putamen and 6 mm spheres for the NAcc. In Figure 13, we show the coordinates in MNI space for each ROI as well as it's volume and number of voxels. Using these ROIs we extracted the weighted beta values for each epoch-condition pair as well as contrast values for each participant. We only analyzed *correct* trials as we did not have sufficient error trials across all participants to examine these reliably.

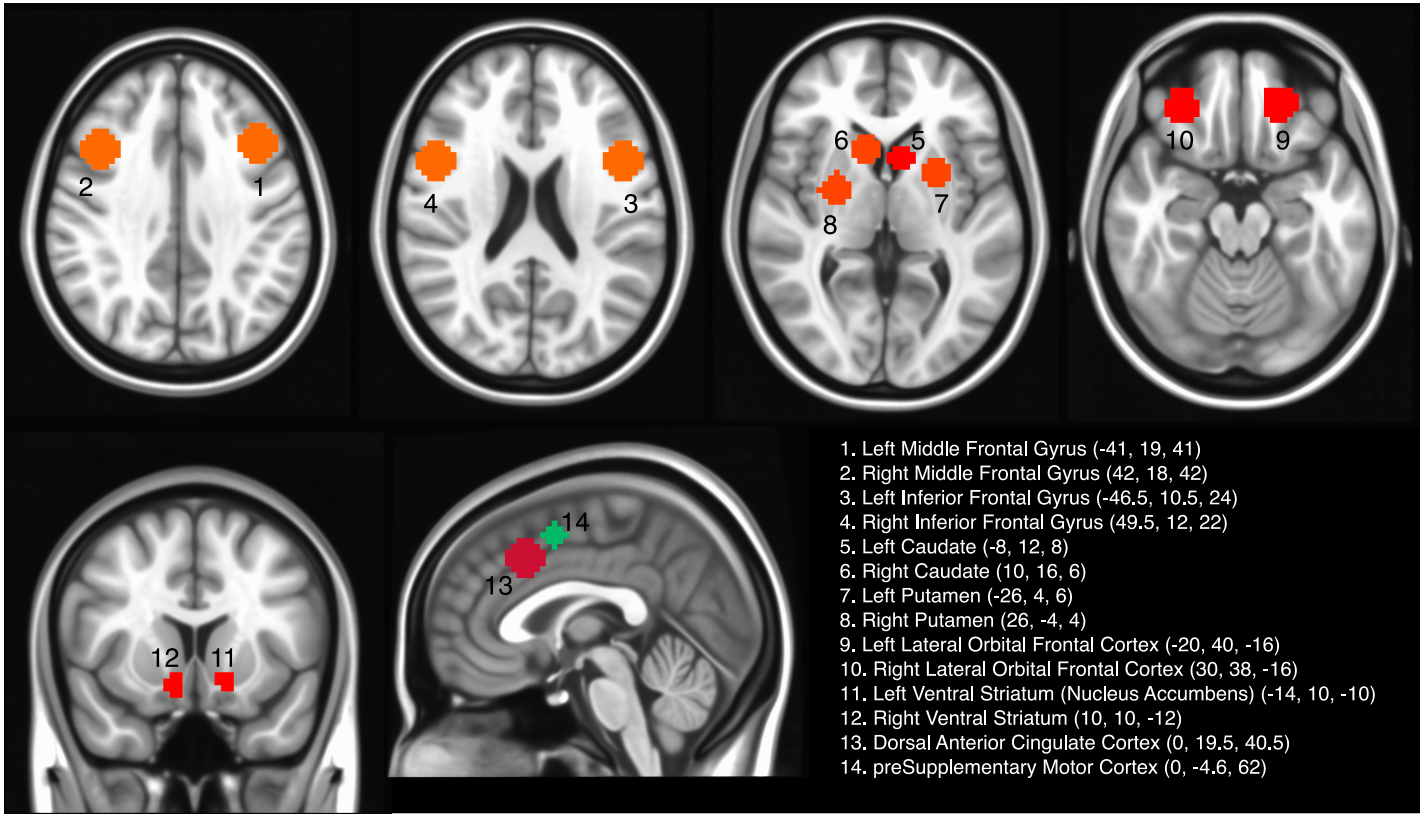

Figure 13. *A priori* regions of interest
Using the Neurosynth platform (Neurosynth.org, (Yarkoni, et al., 2011)), we identified regions previously implicated in incentive processing and cognitive control in adolescence. Images are shown in radiological view (Left = Right). Coordinates of central voxels for each ROI sphere are given in MNI space.

We used R (an open-source statistical program; R Development Core Team, 2009) for our group level analyses. We first ran several model-fit analyses to determine the best fit for the age variable. We determined the optimally fitting model across all ROIs on the basis of the Akaike Information Criterion (AIC) model fit index. This was selected because of its use in other developmental studies that compared different shapes across development (Kail & Ferrer, 2007). We compared inverse, linear and quadratic age models. The AIC model fit index was selected because it allows for comparison of models that are not nested such as the linear and inverse age models as well as allows for comparing across models that have different number of parameters such as the linear and quadratic models. Lower AIC values reflect better model fit to the data. Given evidence of additive allelic influences of the genes of interest, genotype was coded as an ordinal factor reflecting increased number of DA availability for *COMT* (met/met:2, val/met:1, val/val: 0), *MAOA* (3R/3R: 2, 3R/4R: 1, 4R/4R:0) and *DAT1* (9R/10R:0 & 10R/10R:1). Due to differences in number of participants in each genotype group, orthogonal polynomial coefficients for each factor were weighted to reflect unequal sample sizes (Gaito, 1977). The multilocus composite score was calculated similar to prior studies (Nikolova, et al., 2011; Stice, et al., 2012), with a summation of allele load (signifying predicted increases in DA availability) across loci for each individual. This resulted in six separate values across participants. Composite values were mean centered and entered as a continuous variable. Final selected mixed effects models were then run using the chosen age model separately for each genotype as well as the composite score. Sex was included as a covariate in all models and subject was included as a random factor. Results were corrected using simultaneous inference tests for parametric models to correct across all regressions (Hothorn, et al., 2008) using the multcomp platform in R.

3.2.10 Variance Analyses

In order to determine if genotype explained *greater* amount of variance in brain function and behavior, above the age effect (of the age model we selected based on the AIC index), we ran step-wise regressions and calculated change in R^2 for all analyses that showed a significant age effect.

3.2.11 Behavioral Analyses

We ran regression models to examine age effects on AS latencies during *correct* trials as well as AS response rate. AIC values were used to determine which age effect (linear, inverse or quadratic) best fit the data. We then ran linear mixed-model analyses with age, genotype and valence (reward, neutral, loss) as fixed factors and subject as a random factor. We used Bonferroni-correction to account for multiple comparisons: p-value (0.05/3 loci + Composite score = 0.0125).

We also ran regression analyses with the self-report sensation seeking scale (and subscales) as the outcome variables, with age and genotype as fixed factors and subject as a random factor. We used Bonferroni-correction to account for multiple comparisons: p-value (0.05/5 subscales/3 loci + Composite score = 0.0025).

3.3 RESULTS

3.3.1 Pre-scan Assessments

There were no differences in WASI scores across age or between genotype groups (all p's > 0.1). We found no differences across age or between genotype in how participants rated the rewards (p's > 0.5, Mean: 2.23(1.56) on a scale of 1-7). The mean rating score suggested that the reward was rated subjectively high across all participants, with most participants giving the reward a rating between 1 and 3. 6 participants gave a rating of 6 and just 1 gave a rating of 7.

AIC indices for the sensation seeking scales indicated that the inverse model was the best fit over linear and quadratic models. We looked for effects across the total sensation seeking score as well as all the subscales. Across age, there was a significant decelerating positive relationship between age and the total Sensation Seeking Scale (B = -144.741, t (120) = -3.722, p = 0.0003) as well as the Thrill and Adventure Seeking subscale (B = -59.1859, t(120) = -3.496, p = 0.000663) (Figure 14). The other three subscales (Boredom, Disinhibition, and Experience-Seeking did not meet corrected significance). There were no effects of genotype or age by genotype interactions on sensation seeking scores. Variance results showed that adding genotype to both the Total and Thrill and Adventure seeking models only marginally increased the amount of variance explained (range in ΔR^2: .007 - .009, p's > .05).

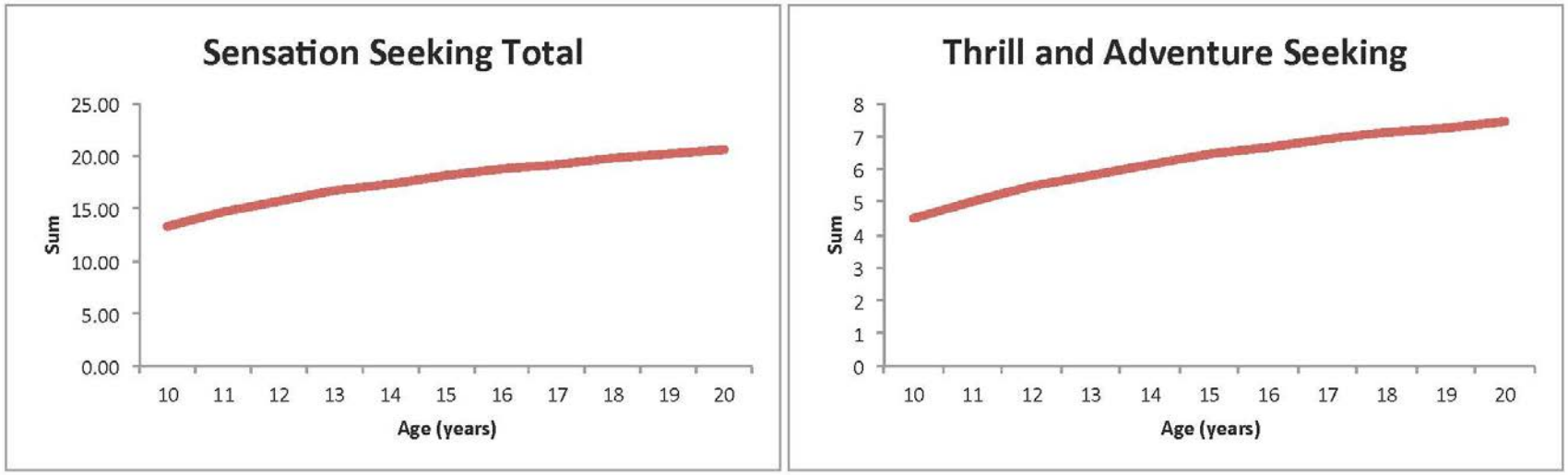

Figure 14. Results of self-report sensation seeking scale
Regression line for the total sensation seeking as well as the Thrill and Adventure Seeking subscale. AIC curves suggested that an inverse function fit the data the best and regression analyses showed a decelerating *increase* in sensation-seeking from 10-20 years of age (p's < .05, Bonferroni corrected).

3.3.2 Antisaccade Latency during correct trials

AIC model indices indicated that the inverse model was the best fit for latency models over the linear and quadratic model. Regression models that included dummy codes for valence (with neutral trials as the reference variable) and age^{-1}, controlling for sex, suggested that there were significant increases in latency to generate a correct response in neutral relative to reward trials (B = -8.4713, t(371) = -4.46, p = 0.00001 and neutral relative to loss trials (B = -7.7627, t(371) = -4.09, p = .00005), independent of age. When changing the reference variable to reward or loss, we found that there were no significant differences in latencies between rewarded and loss trials (B = +/- 0.7086, p = 0.709). Overall, there was a significant effect of age^{-1} in latencies for neutral (B = 1968.2855, t(371) = 4.72, p = 0.000003), reward (B = 1954.0362, t(371) = 4.68, p = .000004), and loss trials (B = 1916.6915, t(371) = 4.59, p = .000005) (Figure 15). Suggesting a decelerating decline in latencies across age. There were no age by valence interactions in latencies (p's > .5). Regression analyses with each genotype showed that there were no effects of any of *COMT*, *DAT1*, *MAOA* or the Composite score on latency (p's > .05). Genotype did not significantly explain the variance above the age^{-1} model for AS latencies (range ΔR^2 : -.01 - .007, p's > .05).

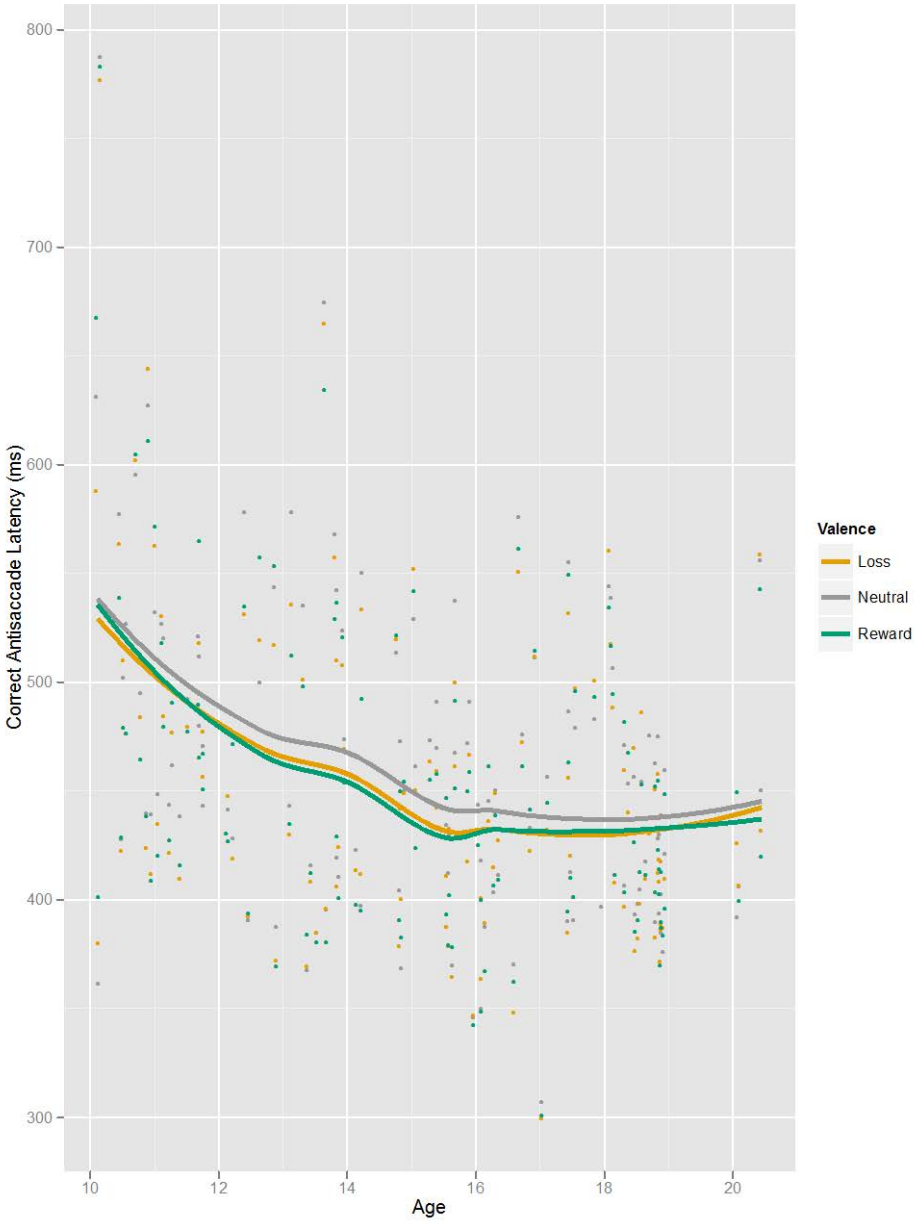

Figure 15. Antisaccade latencies during correct trials (in ms).
Raw data with superimposed loess lines suggest an inverse function best fits the model. Regression results showed that latencies (independent of valence) decreased across age with the steepest decline in early adolescence relative to later. In addition, *neutral* trials (gray line) resulted in longer reaction times than reward (green line) or loss (orange line) (p's > .05, corrected).

3.3.3 Antisaccade Response Rate

AIC model indices indicated that the inverse model was the best fit for percent correct over linear or quadratic. A regression model that included valence (dummy-coded with neutral trials as reference), age^{-1}, controlling for sex, demonstrated a significant difference between neutral and reward trials (B = 0.0263, t(371) = 4.65, p = .000005) and neutral and loss trials (B = .01289, t(371) = 2.28, p = .0234), independent of age, suggesting that individuals performed better during *reward and loss* trials relative to neutral. When changing the valence reference variable to reward, there was a significant difference in percent correct between reward and loss trials (B = -0.0134, t(371) = -4.65, p = .0182) suggesting that individuals performed better during *reward* trials relative to loss trials. There were also significant age^{-1} effects for neutral trials (B = -3.259, t(371) = -5.37, p = .0000001), reward trials (B = -2.783, t(371) = -4.58, p = .000006), and loss trials (B = -3.5204, t(371) = -5.79, p = .00000001) (Figure 16). There were no significant age^{-1} by valence interactions in percent correct values.

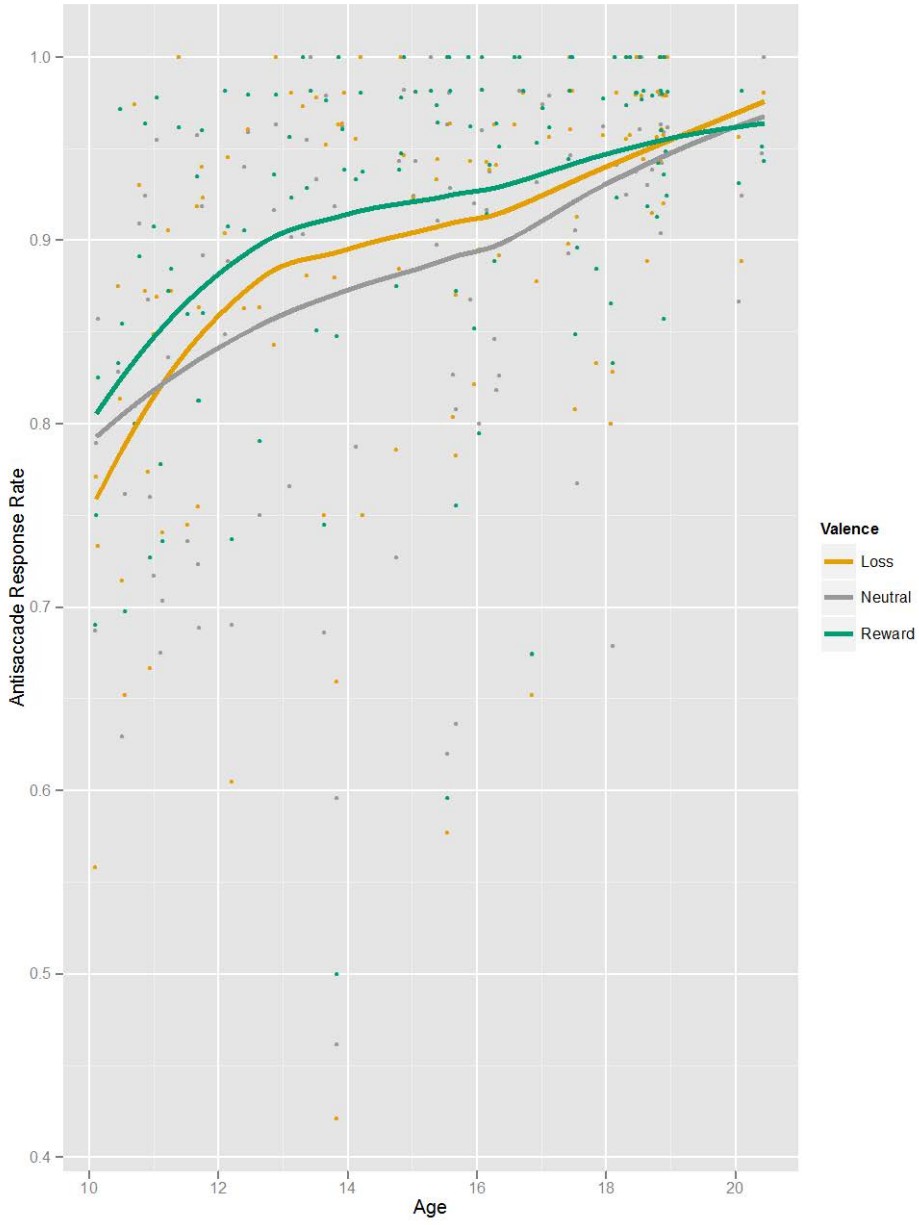

Figure 16. Antisaccade response rate
Raw data with superimposed loess lines suggest an inverse function best fits the model. Regression results showed that proportion of correct trials (independent of valence) increased across age with the steepest rise in early adolescence relative to later. In addition, we found a significant effect of valence. Neutral trials resulted in the lowest proportion of correct trials, followed by loss trials. Participants performed the best during *rewarded* trials (p's > .05, corrected).

Regression models that included genotypes for *COMT, DAT1,* and *MAOA* showed no significant genotype effects or age^{-1} by genotype or age^{-1} by genotype by valence interactions. Analyses that included the Composite score showed no significant effect of the Composite score or Composite by age^{-1} interactions. However, a significant Composite score by age^{-1} by valence interaction (B = 1.5895, t(371) = 2.85, p = .0046) suggests that earlier in adolescence, there is a valence (loss versus reward) by genotype interaction that converges into late adolescence, where younger adolescents with the lowest composite scores (least DA availability) perform better during loss trials than reward, an effect that converges with an increase in composite score (Figure 3.5). In order to assess if gene effects were significant early in adolescence relative to late , we conducted post-hoc simple effects analyses in individuals 10-12 years old and 18-20 years old for behavioral accuracy in the difference between reward and loss trials. We found a significant effect of composite score in *younger* individuals (B = 0.0594, t = 2.51, p = 0.015), but not older (p > 0.05) (Figure 17). Lastly, variance results showed that adding genotype and age^{-1} by genotype interactions to the age^{-1} model did not significantly increase the variance explained (range ΔR^2 : .001 - .007, p's > .05).

Figure 17. Effect of composite score on AS response rate
Regression lines showing the effect of the multilocus composite score on AS response rate during *reward* and *loss trials.* Top graphs show age (x-axis) and genotype (purple lines) separately for each valence. For visualization purposes, the bottom graph shows a *difference* score in performance between rewarded and loss trials and regression lines for each genotype group across age. A significant age^{-1} by composite score by valence interaction suggested that individuals with *decreased* DA showed increased performance during reward trials relative to neutral relative to individuals with *increased* DA ($p = .004$). This effect was significant early in adolescence and converged into late adolescence. The black asterisk denotes the main effect of the Composite score in younger individuals (10-12 years).

3.3.4 fMRI Results: Cue Epoch

Across reward epochs and ROIs, AIC model indices indicated that the inverse of age (age^{-1}) was a better fit than quadratic or linear age models. We found increased activity during *loss* trials relative to neutral (B = 0.02374, t = -3.448, p = .000631) and *loss* trials relative to reward in left MFG (B = 0.03759, t = 5.385, p = 1.3e-07).We also found a significant difference between reward and loss trials in the preSMA (B = 0.0838, t = 13.897, p = 2e-16), and between reward and loss trials in the right MFG (B = 0.029, t = 3.893, p = .0001). Across these significant ROIs, loss trials showed *increased activity* (Figure 18).

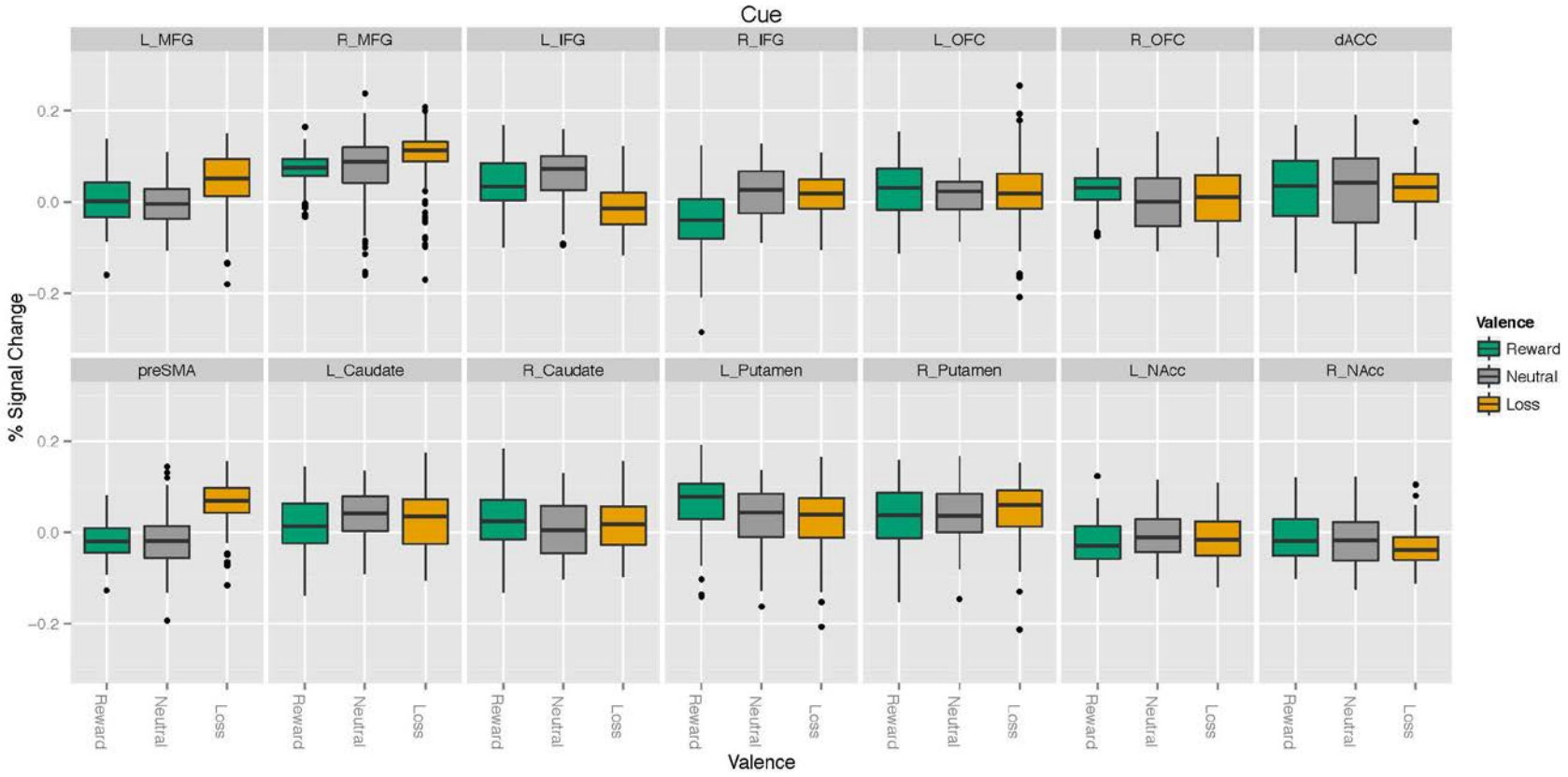

Figure 18. Brain activity for each valence condition during the cue phase, across participants
Only the preSMA and MFG showed a significant valence effect, increasing activity for *loss trials*

We found an age related decline in the contrast between reward and loss trials in the right putamen (B = 1.38826, Z = 3.510, p = .0219, corrected) and left caudate (B = 1.34898, t = 3.411, p = 0.0314, corrected) suggesting a decelerating linear decrease in the difference between reward and loss trials across adolescence (Figure 19).

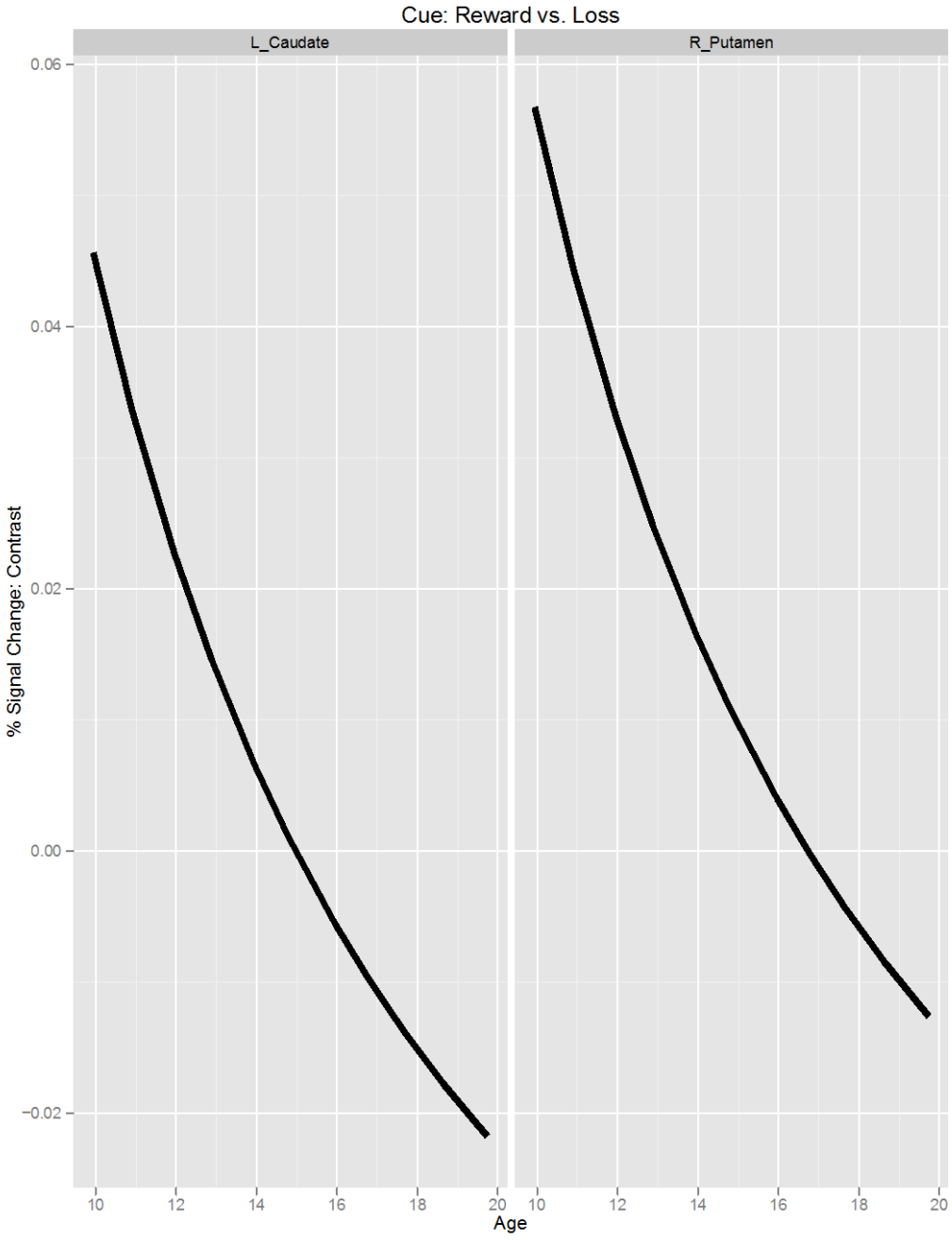

Figure 19. Contrast between reward and loss cues in dorsal striatum
Regression lines showing a *decline* in the contrast between rewarded and loss trials in left caudate and right putamen across adolescence. Younger individuals show a larger response to reward cues relative to loss cues than older individuals.

Results of the models including genotype and the Composite score showed no within-condition genotype or age by genotype interactions during the cue phase. There were no significant increases in variability explained by genotype above age^{-1} in any of the ROIs that had significant age effects.

3.3.5 fMRI Results: Preparatory/Reward Anticipation Epoch

During the response preparation/reward anticipation epoch, we found significant overall effects of Valence (using the Neutral condition as the reference) in the preSMA with *increased* activity during Loss trials relative to Neutral trials (B = -0.0208, t = -3.458, p = .0006) and loss trials relative to reward trials (B = 0.077, t = 12.354, p = 2e-16). *Increased* activity during reward (B = 0.026, t = 3.498, p = 0.0005) and loss (B = 0.0700, t = 9.52, p = 2e-16) relative to neutral in left MFG. We also found increased activity during loss relative to reward (B = 0.044, t = 6.022, p = 4.19e-09). in left MFG . Lastly, we found increased activity in right OFC during reward trials relative to neutral (B = 0.0323, t= 4.572, p = 6.63e-06) (Figure 20).

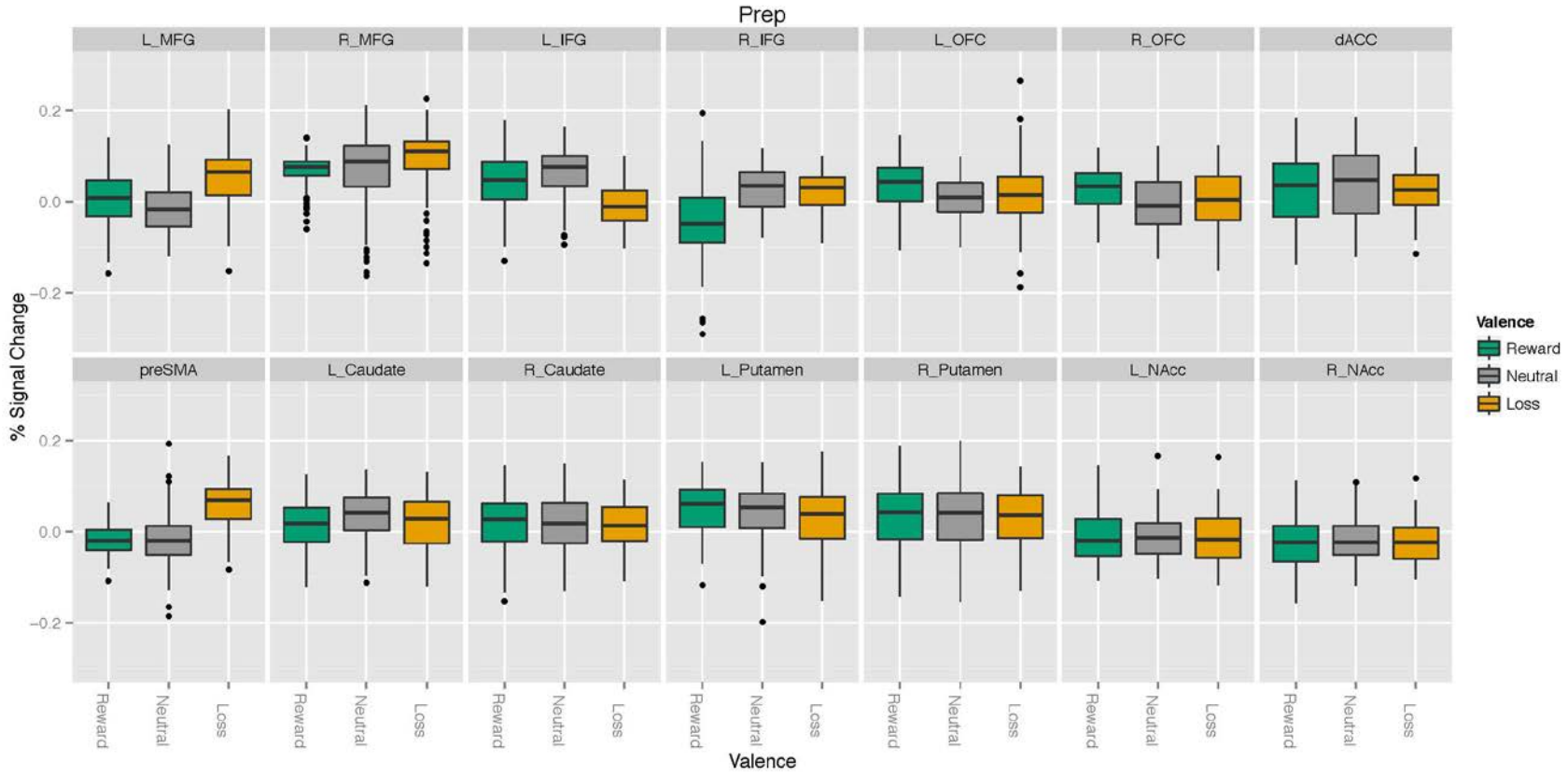

Figure 20. Brain activity for each valence condition during the preparatory phase, across participants
The preSMA showed a significant increase in activity during *loss* trials relative to reward or neutral. In addition, reward and loss trials elicited a greater response in left MFG relative to neutral, with the greatest response during loss trials. Lastly, the left OFC was engaged more for reward trials relative to neutral

We found no age effects during the preparatory phase across any of the 14 ROIs.

Results of the models including genotype and the Composite score showed no within-condition genotype or age by genotype interactions during the preparatory phase. However, we found a significant age^{-1} by Composite score interaction in the left NAcc in the contrast between reward and neutral trials (B = 2.78206, Z = 3.341, p = 0.0401, corrected). Post-hoc simple effects analyses showed that older individuals (18-20) showed a significant effect of composite score (B = 0.0611, t = 2.61, p = 0.014), whereas younger individuals (10-12) did not. There was a greater increase in the difference in activation between reward and neutral trials across age by individuals with relatively *increasing* levels of DA (Figure 21).

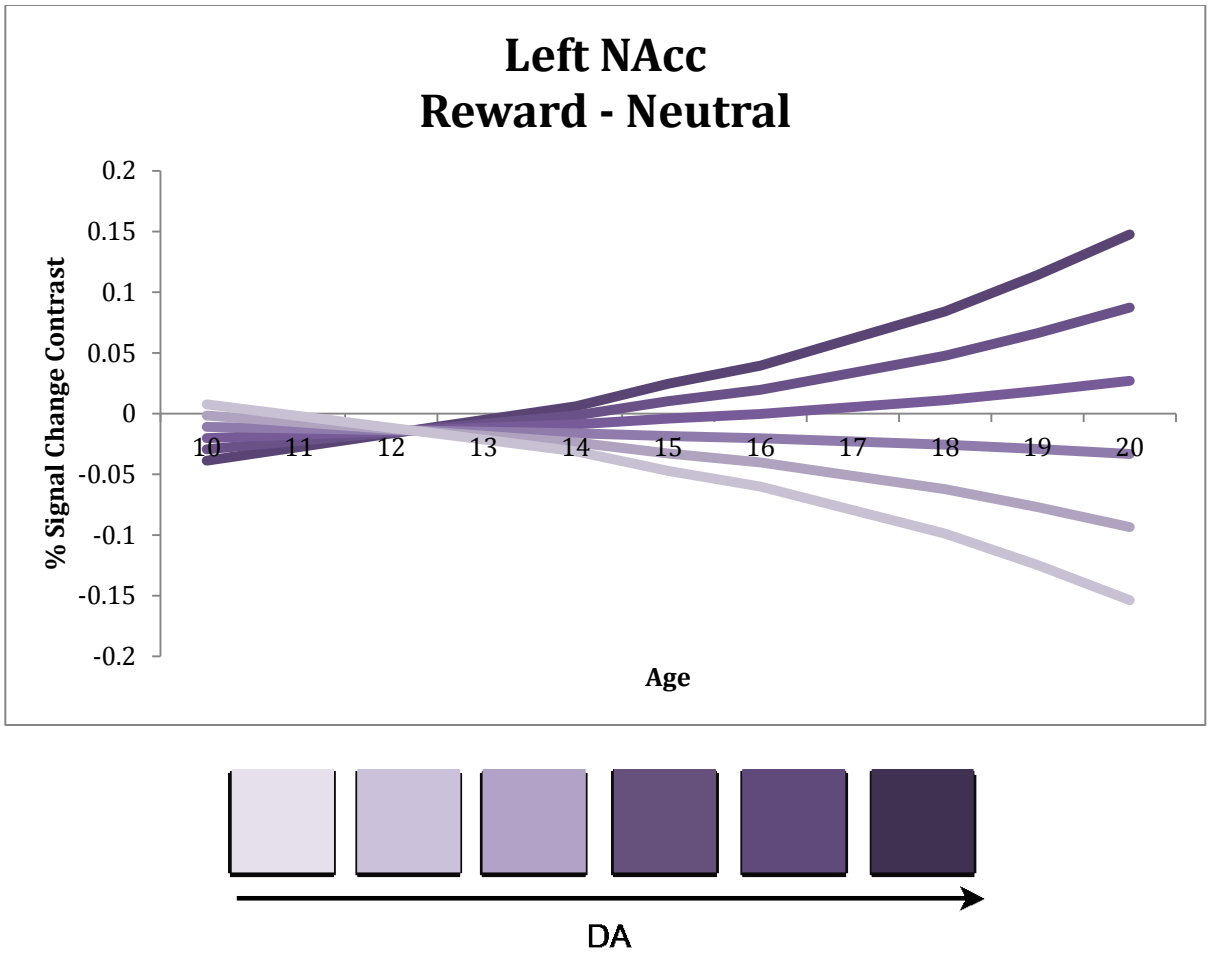

Figure 21. Effect of multilocus composite score on the contrast between reward and neutral preparatory phases in left NAcc.
Age^{-1} by composite score results showed that individuals with increasing DA showed a larger response to reward trials relative to neutral, whereas individuals with decreasing DA showed the opposite. These gene effects were only apparent in *older* individuals, but not younger.

3.3.6 fMRI Results: Antisaccade Response/Reward Receipt Epoch

We found significant valence effects during the saccade/reward receipt stage of the task (using Neutral as a reference variable) in the right OFC with reward trials resulting in increased activity relative to neutral trials (B = 0.0302, t = 4.157, p = 4.02e-05). We also found increased activity during reward trials relative to loss trials in left putamen (B = -0.0327, t = -3.731, p = 0.0002) (Figure 22).

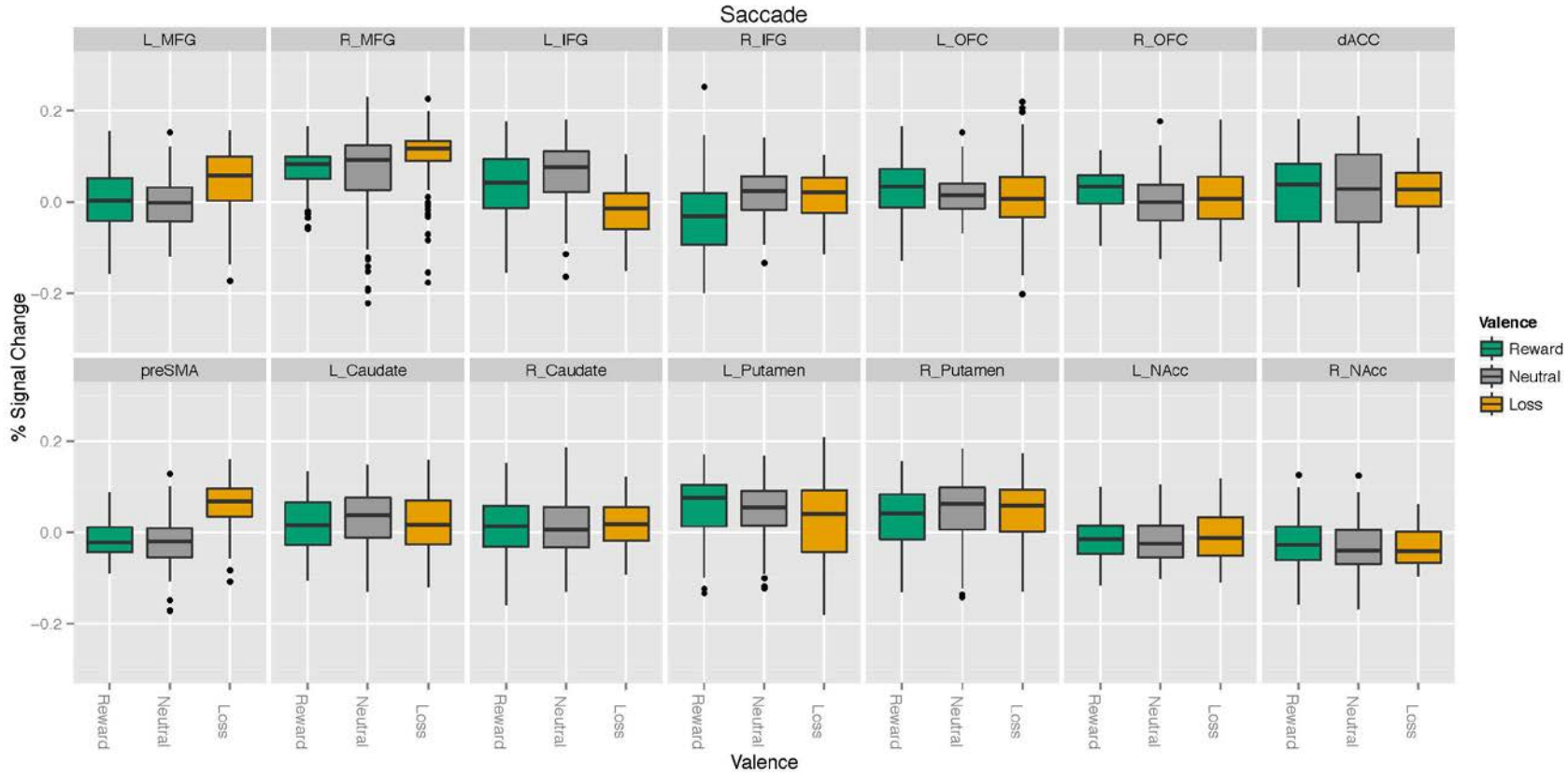

Figure 22. Brain activity for each valence condition during the saccade/reward outcome phase, across participants
The preSMA showed a significant increase in activity during *loss* trials relative to reward or neutral. In addition, reward and loss trials elicited a greater response in left MFG relative to neutral, with the greatest response during loss trials. Lastly, the left OFC was engaged more for reward trials relative to neutral.

We found no age differences across the 14 ROIs during the reward receipt phase.

We found a significant age^{-1} by Composite score interaction in the left OFC in the contrast between reward and neutral trials (B = 2.1608, Z = 3.057, p = .00244, corrected). Simple effects analyses at the end of the age spectrum (10-12 and 18-20) showed a significant main effect of composite score in the reward vs. loss contrast in younger individuals (B = -0.05766, t = -3.199, p = 0.00385) and the opposite pattern in older individuals (B = 0.06, t = 2.94, p = 004). Individuals with *decreased* DA availability showed relatively increased activation for rewarded outcomes relative to no-loss outcomes, an effect that significantly decreased with age, whereas individuals with *increased* DA availability showed the opposite (Figure 23).

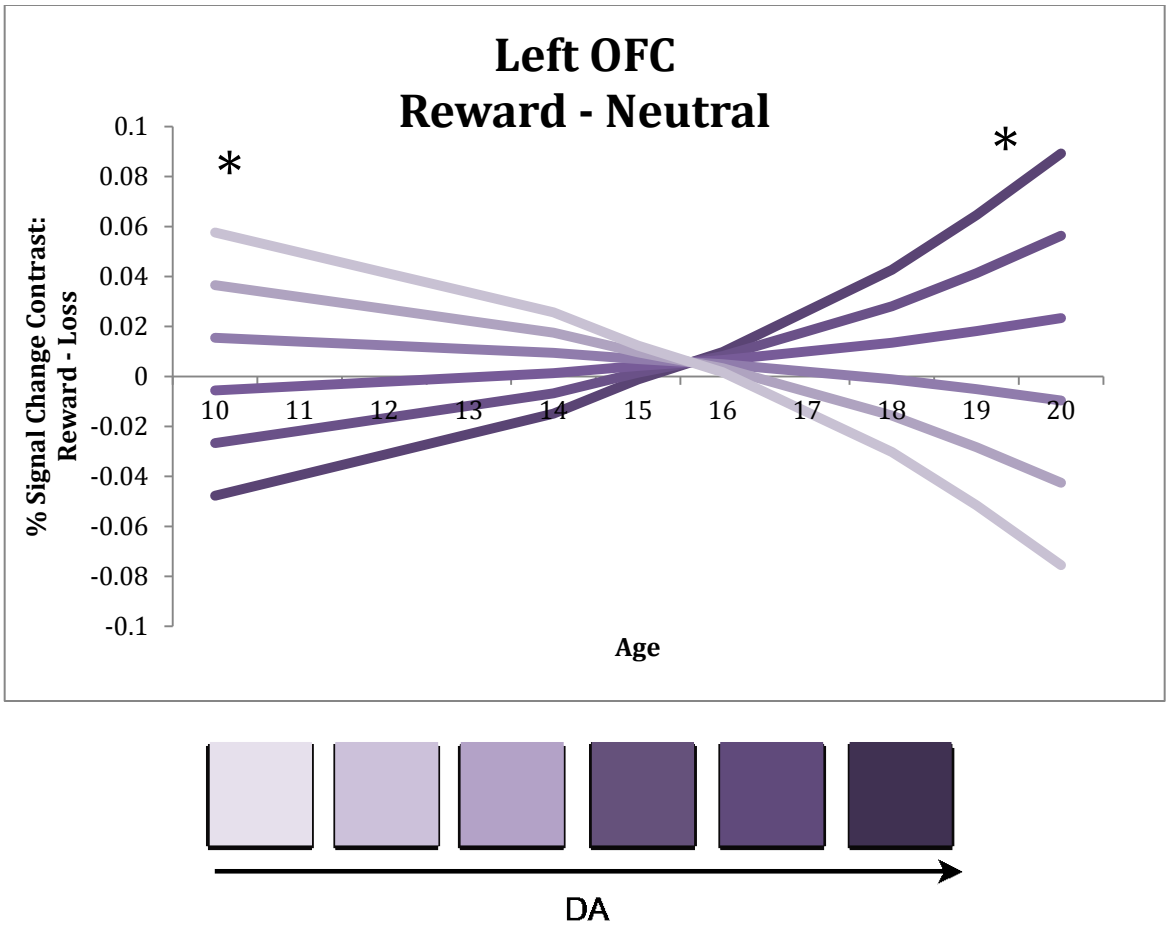

Figure 23. Effect of multilocus composite score on the contrast between reward and neutral reward outcome phases in left OFC

Age^{-1} by composite score results showed that individuals with increasing DA showed a larger response to reward trials relative to neutral in later adolescence/early adulthood, whereas individuals with decreasing DA showed an increase in the difference between reward and neutral trials in early adolescence.

3.4 DISCUSSION

We conducted a fast event related fMRI on healthy participants between the ages of 10 and 20 while they preformed an incentive antisaccade task with reward, neutral or loss contingencies. We used a point-based system and allowed individuals to choose their own reward (contingent on performance) in order to equate subjective rating of incentive value. The design of the task allowed us to separate reward cue, anticipation and outcome. We sought to characterize 1) developmental change in brain function and behavior underlying the influence of incentives on cognitive control of behavior, 2) how changes in DA availability may influence brain function and behavior and 3) how changes in DA availability moderates the effects of age on brain function and behavior. Effects are discussed in more detail below.

3.4.1 Influence of Incentives on Antisaccade Behavior

Consistent with prior studies (Geier, et al., 2010; Padmanabhan, 2011), we found a significant effect of reward incentive on AS latency, with rewarded trials resulting in decreased reaction time to initiate a saccade than neutral. We also found a significant effect of loss trials relative to neutral. Similarly, we found that incentive contingencies (both loss and reward) resulted in *improved* rates of correct trials relative to neutral trials, and that reward contingencies resulted in improved performance relative to loss. This suggests that placing incentive contingencies on behavior do in fact improve inhibitory control (better and faster performance) and that the potential for reward results in improved performance relative to the potential for loss. In addition, we found that both performance rates and latencies significantly changed across age

across all incentive conditions (reward, neutral, loss), following a decelerating improvement (following an inverse function) over adolescence. This finding is also consistent with prior work suggesting that the ability to inhibit prepotent responses improves over adolescence and that rewards continue to play a role in the modulation of inhibitory control into adulthood (Geier, et al., 2010; Luna, et al., 2004). We also found a significant Composite score by age by valence condition on AS performance, suggesting that better performance for reward trials relative to loss trials over adolescence was moderated by DA availability. In early adolescence, individuals with relatively decreasing levels of DA availability performed significantly better during reward trials than loss trials. In adulthood, the difference between reward and loss trials converged across genotypes. The parametric modulation of an increased discrimination between reward and loss trials by DA availability early in adolescence suggests a particular *sensitivity* to rewards relative to loss in line with prior research suggesting that children and adolescents tend to be *less risk aversive* than adults and more approach oriented. Our findings suggest that DA availability moderates this effect. Prior studies have demonstrated that DA neurons respond to rewarding versus aversive outcomes differently (Kim, Wood, & Moghaddam, 2012). It is possible that young individuals with decreased tonic DA availability (as measured by genotype) show increased phasic response to rewards relative to punishment, and this drives better performance during rewarded trials, and worse performance during punishment trials. Additionally, it has been proposed that decreases in phasic DA (perhaps as a result of increased tonic DA availability) supports punishment-based learning through activation of the indirect pathway (Frank, 2005), which may account for individuals with relatively increased DA availability performing as well on loss trials as on reward (Cools, 2008).

3.4.2 Influence of incentives on brain function across adolescence

Independent of age, within each of our 14 ROIs, we found significant valence effects in both cognitive control and reward regions. Importantly, the cortical brain regions involved in both inhibitory and motor processes (MFG, preSMA) showed a heightened response during loss trials relative to reward or neutral, an effect that was seen across epochs. Increased cortical activity during potential loss or punishment trials may be indicative of increased "effort" to correctly perform the task to avoid loss. In addition, reward trials elicited an increased response in putamen during cue and reward receipt phases and OFC during the reward anticipation/preparatory and outcome/saccade response phase relative to neutral or loss trials. The putamen and OFC are both involved in rewarded decision making, with the OFC being involved more during outcomes (Liu, Hairston, Schrier, & Fan, 2011) and the putamen during anticipation (Kimura, Yamada, & Matsumoto, 2003).

We further found an age effect in the contrast between reward and loss trials in the caudate and putamen during cue suggesting that the difference decreased with age (i.e. younger adolescents showed a larger increase for reward trials relative to loss than older individuals). This increased reward distinction in the putamen may reflect a particular sensitivity in young adolescents to rewards (and less so to punishment) consistent with prior findings that sensitivity to punishment and risk aversion is greater in adulthood than childhood or adolescence (Ernst, et al., 2006; Paulsen, Carter, Platt, Huettel, & Brannon, 2011) and may be mediated by striatal responsivity.

Although the majority of the reward processing literature has suggested that the NAcc is engaged during the anticipation of rewards, and is generally hyperactive in adolescence relative to adulthood, we did not see any overall developmental change in the NAcc or an overall effect

of valence. Although, some studies have found diminished NACC activity in adolescence during reward anticipation (Bjork, et al., 2004; Bjork, et al., 2010). It is possible that lack of overall developmental differences in the NAcc during this paradigm was due to equating subjective reward value across participants. Our prior studies that showed increase NAcc response in adolescence during rewarded trials used monetary incentives and do not typically have punishment contingencies (Geier, Terwilliger, Teslovich, Velanova, & Luna, 2009; Padmanabhan, et al., 2011), placing the reward trials in this study in a different context.

3.4.3 Influence of DA availability on reward processing and inhibitory control over adolescence

We did not find any genotype or age by genotype effects for any of the 3 genetic loci we studied, consistent with prior research using different reward paradigms in both adolescents and adults (Nikolova, et al., 2011; Stice, et al., 2012), further strengthening the notion that single genes with relatively small effects may confer a very small portion of the variability in brain function. Our multilocus composite score, which provided an overall index of DA availability as a function of all three DA clearance genes showed a significant interaction with age and valence during the prep phase in the NAcc and age and valence during the reward outcome phase in the OFC.

In the left NAcc, we saw a significant effect of composite score in older individuals with increasing DA levels relative to younger (who showed no DA-related differences) in the contrast between reward and neutral trials. That is, older individuals showed an increased response in the NAcc during rewarded trials relative to neutral and this effect was moderated by genotype, with individuals with relative increased DA availability showed an increase in NAcc activity over age

and individuals with decreasing DA showed the opposite. The NAcc is highly innervated by DA neurons from the VTA and projects to various areas of cortex, giving it a central role in the processing of rewards and influencing motor output (Mogenson, Jones, & Yim, 1980). Prior studies showed that adults with increasing DA signaling as measured with a multilocus composite score show increased NAcc reactivity to reward outcomes relative to a control (neutral) condition (Nikolova, et al., 2011). Interestingly, we found an increased sensitivity to rewards relative to neutral trials in the NAcc in older individuals relative to younger, rather than a peak in sensitivity in middle adolescence consistent with the literature. However, we also found that self-reported sensation-seeking followed a decelerating linear increase in our cohort of participants, which was also counter to prior research suggesting a peak in sensation seeking in middle adolescence (Steinberg, et al., 2008). Although we did not find a genotype effect with the sensation-seeking scales, likely due to our relatively small sample size to detect gene effects on behavior, a prior study found an effect of a multilocus composite score on sensation-seeking traits in 635 adults, with individuals with increased DA signaling (as measured by 273 SNPs from eight DA genes) scoring higher than individuals with decreased DA function (Derringer et al., 2010). Therefore, increased DA signaling may lead to increased reward-reactivity in NAcc relative to neutral, which may underlie increased sensation-seeking traits.

During the saccade/reward outcome phase of the task, we saw an age by composite score by valence interaction in the OFC. Importantly we found a composite score effect in early adolescence relative to late adolescence/early adulthood where younger individuals with decreased DA availability showed heightened activation for reward versus neutral trials and the opposite pattern in older individuals (with increased DA availability resulting in an increased response to rewarded relative to neutral trials). The OFC, which is highly innervated by VTA

DA neurons, provides top down regulation of DA activity in midbrain, and involved in reward *assessment*, prediction errors, and outcomes (Lodge, 2011; Takahashi et al., 2009). In addition, it is thought that the OFC processes rewards differently in adolescents than in adults (Galvan, et al., 2006), as regulation of neuronal circuits are still immature. We demonstrated a significant interaction between DA availability and brain activity for reward relative to neutral trials Younger adolescents (10-12 years) showed a significant Composite score effect, with *decreased* overall DA availability resulting in an increased response during reward relative to neutral trials, as spontaneous DA activity is higher in adolescence than adults (McCutcheon & Marinelli, 2009), as are midbrain DA projections to PFC (Berger, Verney, Febvret, Vigny, & Helle, 1985; Kalsbeek, Voorn, Buijs, Pool, & Uylings, 1988; Lambe, et al., 2000; Rosenberg & Lewis, 1995), showing both peaks in adolescence as well as monotonic increases from adolescence to adulthood, and increases in receptor density in adolescence relative to adulthood, it is possible that younger individuals with relatively higher DA availability exhibit decreased reward sensitivity relative to adolescents with decreased DA availability (but still increased relative to adults). As the DA system becomes more stable into adulthood, these individuals (with higher DA availability as measured with genotype) may improve in the ability to react to rewards in the OFC, consistent with the adult literature, whereas individuals with relatively lower DA, show a decrease in this ability into adulthood. Lower DA function in PFC in adulthood has been previously linked to altered OFC functioning (Mizoguchi, Shoji, Tanaka, & Tabira, 2010; Zeeb, Floresco, & Winstanley, 2010), and is mediated by individual differences in traits that involve DA function (Winstanley et al., 2010). Although future work is necessary to establish a direct connection between OFC response to rewards and it's modulation by changing DA influence over adolescence, a relative difference in the variability as a function of genotype earlier in

development relative to later is akin with our proposed model (Figure 1.1) suggesting that certain individuals might show different predispositions as a function of both genetically mediated DA function as well as developmental stage. Interestingly, the switch in relative influence of DA availability on OFC signaling occurred in middle adolescence, when much of the research identifies as a crucial time of change in DA functioning (Luciana, et al., 2012). Mid-adolescence is often identified as the time when adolescents begin to reach adult levels of cognitive control (Luna, et al., 2004), and demonstrate peaks in reward sensitivity (Casey, et al., 2008). Although speculative, it is possible that dramatic changes in the DA system in middle adolescence (perhaps concurrent with pubertal timing and other major maturational events) lead to a fundamental change in incentive-related processing, especially in executive control regions.

4.0 GENERAL DISCUSSION

4.1 SUMMARY AND INTERPRETATIONS

The main aim of this dissertation was to characterize the influence of dopamine availability on frontostriatal brain function over adolescence. To this end, we conducted two studies to 1) examining the integrity of frontostriatal networks over adolescence using resting state functional connectivity and 2) assessing the influence of incentives (reward and loss) on cognitive control of behavior in the adolescent brain. We measured relative synaptic DA availability by genotyping individuals for polymorphisms in critical DA clearance genes that have known functional significance (*COMT* val158met, *MAOA* u-VNTR, *DAT1* 3'-VNTR). In addition, we calculated a multilocus composite score, by assigning each allele in each gene with a value corresponding with a *relative* amount of DA availability, summing these values across genes for each participant.

We did not see any patterns of activity or connectivity that followed a quadratic-shaped trajectory with age, indicative of the developmental "peaks" in DA availability from animal studies (Wahlstrom, White, et al., 2010). It is possible that our age range was too narrow to adequately capture a quadratic effect, as our oldest participants were at the very tail end of the human adolescent period. However, overall we were able to show that DA availability as

measured by a combination multiple genetic markers that directly influence extrasynaptic DA clearance moderate age related changes in brain function in frontostriatal circuitry.

Our first study (Chapter 2) examined the integrity of frontostriatal circuitry as measured with intrinsic functional connectivity. We predicted that changes in rsFC as a function of DA levels would speak to the influence of varying levels tonic DA transmission as measured by genotype on coherence between different frontal and striatal regions. We found that the majority of frontostriatal connections did not change over adolescence, suggesting that key connections may be established by late childhood. However, we did see a significant age effect in the connectivity between the caudate and dACC, components of a cognitive control system. This significant age effect was driven by individuals with the lowest relative amount of DA availability, highlighting a potential individual difference in plasticity, and perhaps inefficiency in cortical-subcortical processing in individuals with less *DA* early in adolescence that stabilizes into adulthood.

In our second study (Chapter 3), we explored the influence of incentives on cognitive control of behavior using a rewarded AS task, using the same genetic loci and multilocus composite score as we did in Chapter 2. As expected, we found that incentives *did* influence behavior, by decreasing reaction times and increasing response rates across all individuals. Furthermore, we found that inhibitory control improved over adolescence independent of incentives. Interestingly, we found an effect of genotype on AS behavior, in early adolescence. Younger individuals with decreased DA availability performed worse on loss trials relative to reward, an effect that converged in adulthood. It is possible that decreased DA signaling contributes to a relatively diminished loss-aversion relative to reward-seeking in early adolescence. Older individuals did not show this effect, although they did show an overall

valence effect (as there was no age by valence interactions). This could be due to ceiling effects in performance that are less perturbed by differences in DA availability.

Contrary to prior research, we did not find any gene effects for any of the individual loci on reward processing or cognitive control. However, we did have two significant gene-related findings in key reward-processing regions, namely the NAcc during reward anticipation and the OFC during *reward receipt.*

Our findings are in line with prior research implicating the NAcc in signaling prior to receiving a reward, engaging preparatory mechanisms to bias behavior towards reward attainment (Knutson & Cooper, 2005). The NAcc, which receives dense DA projections from VTA, and is known to release phasic DA when anticipating reward (e.g.(Sugam, Day, Wightman, & Carelli, 2012)), showed a significant age by Composite score interaction with *adults* showing a significant modulation by genotype during anticipation of reward receipt. These findings are consistent with prior findings of the NAcc differing in activation as a function of increasing DA signaling in adulthood. We did not observe these differences in early adolescence suggesting an immaturity in reward processing, and perhaps a diminished influence of DA modulation of NAcc activity. Importantly, the interaction with age is suggestive of a protracted maturation of reward systems and incentive processing over adolescence that is perhaps in part influenced by DA function. Lastly, we found a significant age by Composite score effect on OFC, a region implicated in the executive assessment of reward, including valence and subjective preference for rewards over non-rewards (Hare, O'Doherty, Camerer, Schultz, & Rangel, 2008; Kringelbach, 2005) signaling during reward receipt. Although we did not find any age effects in OFC, contrary to prior research, we found that a significant moderation by genotype altered age-related patterns as a function of DA availability. This

suggests that changes in brain function (and consequently behavior) might in part be explained by variability in DA signaling, and that the influence of relative DA availability on the brain can change over adolescence into adulthood.

Going back to our initial model, (Figure 1), we demonstrate that there's a distinct and dynamic effect of DA on brain function in frontostriatal circuitry over adolescence. We first observed that in the connectivity between the Caudate and dACC, in brain function during reward anticipation in the NAcc and lastly in the OFC during reward receipt. Our main age by composite score interactions underscore the notion of individual differences in developmental trajectories that may help explain variability in behavior and specific vulnerabilities as a function of differences in neurotransmitter function. That is, a genotype that may be considered risky or suboptimal in early adolescence, may not demonstrate the same negative effects in adulthood (or vice-versa). It is possible that changes in the relative influence of the DA system in the developing brain are a result of compensatory mechanisms coming online to alter trajectories. The DA system is highly dynamic and is thought to be self-regulatory in order to maintain homeostasis in a typical brain. For example, individuals with increased baseline levels of DA also have increased autoreceptor function as a compensatory mechanism (Torstenson et al., 1998). In addition, at the systems level, changes in DA levels in PFC can alter DA signaling in subcortical structures (Meyer-Lindenberg, Kohn, Kolachana, Kippenhan, McInerney-Leo, et al., 2005). Further research should examine the interaction of DA functioning over adolescence and the timing and tempo with which its influence on the brain coincides with other maturational processes, and the complex interactions between the different aspects of the DA system (e.g. transporter and receptor function, projections and feedback loops, and regulatory and compensatory functions).

4.2 LIMITATIONS AND FUTURE DIRECTIONS FOR DEVELOPMENTAL IMAGING GENETICS

Genetic basis for complex behavioral traits is likely a result of allelic variation across many genes, interactions between many genes, as well as interacting environmental factors. Most human genetics research focuses on high frequency alleles, which generally have favorable or neutral effects and explain only a small proportion of the variance in complex disorders or traits. Studies of genetic associations with brain function or behavior may not pinpoint genetic causes of complex disorders to personalize treatment or risk on an individual basis. However, they can aim to better understand the neural pathways and mechanisms underlying disease states and behavior. Imaging genetics with the relative proximity of brain function to the genotype of interest permits gene effects on brain function to be observed in significantly fewer participants than typical behavioral genetics studies. While there are many advantages to an imaging genetics "intermediate phenotype" approach to linking genes to behavior, there are known limitations and methodological considerations that are addressed below.

Systematic non-genetic differences between groups defined by genotype such as sex, IQ, illness, injury, and substance abuse can confound or mask true gene effects and must be controlled. For example, allelic frequencies for both the *COMT val158met* and *DAT1 3' -VNTR* polymorphisms have been found to vary significantly across ethnic groups (Kang, Palmatier, & Kidd, 1999; Palmatier, Kang, & Kidd, 1999). This is referred to as population stratification and in order to control for this, groups should be assessed for ethnic ancestry and distributed equally, or only one ethnic group should be assessed at a time.

Given that many genes likely contribute to brain function and Type I error may be high. To address this issue, Meyer-Lindenberg et al. (2008) assayed 429 SNPs in genes that had no

known associations with brain related functions and scanned 129 participants during a working memory and an emotional paradigm. Results suggested that at conservative statistical thresholds (with multiple comparison corrected thresholds of .05), the rate of positive associations ranged from 0.2 to 4.1%, well below the 5% cutoff for Type I error. This provides evidence that when correct statistical methods are employed; false positive rates are well controlled for in imaging genetics studies.

Interpreting the effects of genetic variations on brain processing requires maximal sensitivity and value of the measures obtained. Therefore, tasks used must reliably and robustly engage circumscribed brain systems and demonstrate variance across participants (Bigos & Hariri, 2007). Munafo et al. (2008) conducted a meta-analysis of studies that have reported associations between the serotonin transporter genotype (5-HTTLPR) and amygdala activation and determined that assuming equal numbers of genotype groups, an imaging genetics study using the 5-HTTLPR and amygdala activation would require a total sample of about 70 participants to achieve .8 power for an alpha power of .05. Similarly, others have suggested that sample sizes of over 25 subjects in each group are necessary in fMRI in order to have adequate reliability (Thirion et al., 2007). Meta-analyses to determine effect sizes of previous studies and ideal sample sizes for future ones is warranted for the *COMT* and *DAT1* polymorphisms, especially given that behavioral findings are mixed (Munafo, Bowes et al. 2005; Barnett, Scoriels et al. 2008) and often underpowered.

Future directions for imaging genetics research should allow for translational work, studying the influence of genetically driven variability in enzyme function in both humans and animal models with the same behavioral/neurofunctional phenotype (i.e. transfer cognitive tasks that are validated in mice to humans) (Casey, Soliman, Bath, & Glatt, 2010). Despite the

translational limitations in these approaches, studies using genetically modified mouse models for key DA genes, including *COMT* and DA receptor partial knockin and knockout mouse models have demonstrated cognitive and behavioral outcomes that may be similar to the resulting phenotypes in humans (for review see (Casey, et al., 2010)). Furthermore, these models, which can be studied across development and have strict control over environmental influences, may provide information on the emergence of cognitive traits, on genetically-mediated variability in these traits, and has potentially significant implications for understanding the variability in adolescent risk taking as well as the developmental trajectory of psychiatric illness pathology and thus point the way towards early intervention and disease modifying approaches.

To date, most imaging genetics studies have focused on associations between single genes and specific brain regions of interest. Given the heterogeneity of complex behaviors, future studies would benefit from applying multimodal approaches that combine brain function and structure at varying spatial and temporal resolutions, assessing behavior using a battery of reliable and well delineated tasks and assessments, using adequate measures of environmental factors, and importantly using a well-defined phenotype of interest. Within a reasonable realm of financial and logistical possibility, more studies of gene-gene and epistatic interactions are warranted. It would be especially interesting to study interactions between genes that influence different neurotransmitter and/or cellular systems, especially in adolescence as the protracted development of many neurotransmitter systems likely have dynamic, interactive effects (Meyer-Lindenberg, 2012).

Not surprisingly so, the study of gene-environment interactions is of crucial interest. Evidence suggests that not only does genetic makeup influence how an individual will react to

their environment, but through epigenetic regulation, the environment may also play a role in which and how genes are expressed and how they in turn influence behavior (Day & Sweatt, 2011). For example, environmental factors such as drug intake or stressful situations can alter hormonal and neurochemical processes, which are especially influential during brain development (L. P. Spear, 2000). This has implications for how environmental factors, interacting with genetic predispositions, may give rise to individual differences in specific traits, as well as lead to vulnerability to psychiatric illness.

Furthermore, given that neurotransmitter systems are expressed throughout the brain and that the study of brain networks are at the forefront of the field of cognitive neuroscience, future imaging genetics studies should employ measures of pathways and connections between brain regions as outcome variables rather than activation in isolated areas (Fornito & Bullmore, 2012), which has been the primary focus of prior imaging genetics research.

Lastly, multimodal approaches (such as combining PET and fMRI) may be fruitful in identifying neurofunctional outcomes at both the cellular and systems level of brain function (Fisher, Munoz, & Hariri, 2008). Building upon and combining existing methodologies will provide unique insight into the biological factors underlying individual differences in behavioral function and dysfunction.

In a developmental context, longitudinal studies, which control between participant variability, are a preferred way to examine genetics effects on developing neural systems underlying normal and abnormal behavior. This approach can help determine how variation in genetic mechanisms affects critical time windows of development during which key brain maturational processes occur. However, cross-sectional developmental studies in a normative population have the advantage of providing findings within a rapid window of study that can

inform longitudinal studies. Elucidating the effects of genetic mechanisms on the developing brain can result in better understanding of the genetically driven variation of DA regulated behaviors. Studying these polymorphisms in the context of frontostriatal neural function can highlight individual differences in this circuitry that contribute to the variability in complex behavior. This can have strong implications for understanding the neurobiology of heightened risk taking during adolescence, vulnerability to psychopathology, and age specific medication effects. Identifying variants that render an individual vulnerable to certain environmental factors, which may be triggered by biological processes through epigenetic mechanisms, and using genetics to better understand the plasticity of a developing system could help shed light on the development of behavioral traits as well as the emergence of psychopathology. Overall, a better characterization of the behavioral phenotype, the endophenotype or intermediate phenotype as well as the specific functional significance of the genetic variant of interest is warranted.

4.3 CONCLUSIONS

We presented a model suggesting that DA-driven function in frontostriatal circuitry would show distinct variability in early adolescence relative to adulthood. Given what we know about the reorganization of the DA system of which *peaks* in DA availability provide one potential mechanism underlying increases in sensation-seeking and risk taking behaviors, we predicted that changes in DA levels would moderate age effects on brain function. Our results indicate that the development of frontal and striatal brain circuits do rely on variability in the DA system as evidenced by changes in brain function over adolescence as a function of increasing or decreasing DA availability. We measured DA availability using functionally significant genetic polymorphisms with known effects on DA clearance proteins. In addition to single genetic loci, we constructed an additive genetic model representing an index of *overall* DA availability. We found that a multilocus composite score explained more of the variability in age related changes in brain function than single loci. Further investigation of adolescent brain function and its moderation by dopamine and other neurotransmitter systems is warranted. By using techniques such as imaging genetics, we can with more precision highlight the *biological basis* of behavioral and brain related immaturities in adolescence and identify the mechanisms that explain variability in both increased risky behaviors in normative development as well as vulnerability for psychopathology at this time. The inability to consistently control behavior concurrent with increased sensation seeking persists in adolescence, leading to a peak in risk taking. Although these behaviors may be mediated by non-biological factors, we must better characterize the biological mechanisms driving these changes in order to fully appreciate their consequences. This dissertation provides some of the initial steps in better understanding the biological bases of variability in brain function over adolescence.

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