Developmental imaging genetics: linking dopamine function to adolescent behavior

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Abstract

Adolescence is a period of development characterized by numerous neurobiological changes that significantly influence behavior and brain function. Adolescence is of particular interest due to the alarming statistics indicating that mortality rates increase two to three-fold during this time compared to childhood, due largely to a peak in risk-taking behaviors resulting from increased impulsivity and sensation seeking. Furthermore, there exists large unexplained variability in these behaviors that are in part mediated by biological factors. Recent advances in molecular genetics and functional neuroimaging have provided a unique and exciting opportunity to noninvasively study the influence of genetic factors on brain function in humans. While genes do not code for specific behaviors, they do determine the structure and function of proteins that are essential to the neuronal processes that underlie behavior. Therefore, studying the interaction of genotype with measures of brain function over development could shed light on critical time points when biologically mediated individual differences in complex behaviors emerge. Here we review animal and human literature examining the neurobiological basis of adolescent development related to dopamine neurotransmission. Dopamine is of critical importance because of (1) its role in cognitive and affective behaviors, (2) its role in the pathogenesis of major psychopathology, and (3) the protracted development of dopamine signaling pathways over adolescence. We will then focus on current research examining the role of dopamine-related genes on brain function. We propose the use of imaging genetics to examine the influence of genetically mediated dopamine variability on brain function during adolescence, keeping in mind the limitations of this approach.

Introduction

In the human lifespan, the adolescent period roughly coincides with the onset of puberty, when key neuroendocrine processes trigger and co-occur with a complex series of biological changes including, significant physical, sexual, neurochemical, neurofunctional, physiological, cardiovascular, and respiratory maturation (Falkner and Tanner 1986; Romeo 2003). These biological changes reciprocally interact with the environment and characterize

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a vulnerable and dynamic period of physical, psychological, and social development (Spear, 2000). Across species and cultures, there are characteristic behaviors during adolescence including peaks in sensation/novelty seeking coupled with diminished levels of harm avoidance, leading to an increase in risky behaviors (Laviola, Macri et al. 2003). Normative increases in sensation/novelty 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, certain behaviors that have high subjective desirability can also expose an individual to harmful consequences (Spear, 2000). Thus, we define risk-taking as engaging in a behavior with potential rewarding outcomes (also known as incentive-driven behavior), but high potential negative consequences. The consequences of risky behaviors that peak in adolescence (e.g. experimentation with drugs and alcohol, reckless driving, and unprotected sex), can be dramatic as mortality and morbidity rates increase significantly from childhood (Dahl 2004). 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 (Pine 2002; Chambers, Taylor et al. 2003; Sisk and Zehr 2005; Paus, Keshavan et al. 2008), the risk factors for which are not fully characterized. In light of this evidence, it is also important to note adolescents are capable of mature decision-making (Paus 2005), abstract thinking, and often engage rational behavior (Steinberg, Cauffman et al. 2009). Thus, many of the classic risk-taking behaviors observed in adolescence are often in the context of highly emotive and/or reward-seeking states (Casey, Getz et al. 2008; Blakemore and Robbins 2012), highlighting a unique and universal biological vulnerability and neuroplasticity that is not fully characterized.

Despite evidence of overall increases in risk taking behaviors in adolescence, with the assumption that each individual is at their own peak in sensation and novelty seeking, there is much variability in adolescent behavior that remains unexplained. That is, while some adolescents are high risk-takers, others are not, and the contexts under which certain individuals engage in risk-taking vary. In recent years, the field of genetics has merged with cognitive neuroscience to examine the neurobiological basis of variability in behavior. This approach, known as 'imaging genetics', is grounded in the idea that brain function and structure can serve as intermediate phenotypes between genes and behavior, given the relative proximity of brain function to the genotype (Hariri and Weinberger 2003).

This review focuses on the influence of the neurotransmitter dopamine and variations in dopamine genes on incentive-driven behaviors in adolescence. We first review the literature on the maturation of key brain systems – namely frontostriatal circuits - and their role in adolescent behavior. The role of dopamine in modulating motivated behaviors and the protracted development of dopamine function through adolescence will be discussed next. Lastly, we focus on a review of imaging genetics studies using common functional polymorphisms in key dopamine signaling genes leading to a proposal for future research in adolescent brain development.

Incentive driven behaviors and frontostriatal circuits in adolescence

Evidence suggests that adolescents tend to both process incentives differently than adults (for reviews see: Geier and Luna (2009; Ernst, Daniele et al. 2011)), leading to suboptimal and often risky decision-making. The framework of adolescent incentive processing is contingent on the idea that adolescents are biased towards potential rewards (Steinberg 2004) and display immature cognitive control (Yurgelun-Todd 2007), with continued maturation in the brain systems that underlie both (Casey, Getz et al. 2008; Ernst and Fudge 2009).

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 prefrontal cortex (PFC) by way of overlapping but functionally segregated pathways (Alexander, DeLong et al. 1986; Postuma and Dagher 2006; Di Martino, Scheres et al. 2008) that are underlie distinct behaviors (Tekin and Cummings 2002). Major frontal-striatal circuits function by way of excitatory projections from frontal regions to specific striatal areas (e.g. dorsolateral PFC to dorsal caudate, lateral OFC to ventromedial caudate, medial OFC to nucleus accumbens) and back via the thalamus. These closed-loop circuits result in two major pathways; direct and indirect. The direct pathway, which disinhibits the thalamus, involves GABAergic projections from striatum to midbrain to the internal segment of the globus pallidus to the thalamus. The indirect pathway consists of GABAergic projections from striatum to the globus pallidus externa to the subthalamic nucleus, finally exciting inhibitory neurons in the globus pallidus interna, which inhibit the thalamus. Thus, favored behaviors are activated via the direct pathway and the indirect pathway inhibits less desirable and competing actions. Thus, immaturities and disturbances in the function of frontostriatal circuits may result in competition between the direct and indirect pathways, leading to suboptimal behaviors.

To this end, neurobiological models of adolescent development suggest that an over active adolescent incentive system, driven by the striatum, with a still maturing cognitive system, driven by the PFC, 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 ((Nelson, Leibenluft et al. 2005; Ernst, Pine et al. 2006; Casey, Getz et al. 2008), for a summary of these models see Sturman and Moghaddam, (2011)). Indeed, functional neuroimaging studies of incentive processing demonstrate differential striatal and PFC activation in adolescence relative to adulthood (Bjork, Knutson et al. 2004; Ernst, Nelson et al. 2005; Galvan, Hare et al. 2006; Bjork, Smith et al. 2010; van Leijenhorst, Moor et al. 2010; Padmanabhan 2011), with the majority of studies reporting an increase in striatal activation, coupled with decreases in prefrontal recruitment. Furthermore, functional connectivity studies suggest that the integration and coordination between brain regions, including subcortical to cortical connections, become more refined and efficient over adolescence, leading to reduced task-irrelevant connections, strengthening of connections supporting goal-directed actions, and elimination of redundant connections (Durston, Davidson et al. 2006; Liston, Watts et al. 2006; Fair, Cohen et al. 2009; Stevens, Pearlson et al. 2009; Hwang, Velanova et al. 2010). Animal and post-mortem human

literature suggests an overexpression of receptors for serotonin, dopamine, adenergic, and endocannabinoids (Lidow and Rakic 1992), a peak in the density of interneurons (Anderson, Classey et al. 1995; Lewis 1997; Erickson and Lewis 2002), and an increase in levels of GABA (Hedner, Iversen et al. 1984). These changes alter the excitatory-inhibitory balance in neuronal signaling that refine controlled processing into adulthood. Lastly, increased myelination in cortical to subcortical axons, changes in axon caliber, pruning of synapses and receptors, cell shrinkage, and glial changes (Yakovlev and Lecours 1967; Rakic, Bourgeois et al. 1986; Benes, Turtle et al. 1994; Andersen 2003) refine the developing brain and strengthen and consolidate highly used connections, while weakening or eliminating redundant or weakly used connections through unique experiences ((Huttenlocher 1990; Jernigan, Trauner et al. 1991; Pfefferbaum, Mathalon et al. 1994; Giedd, Blumenthal et al. 1999), for review see: (Paus 2005)). Taken together, the current literature highlights that immaturities in the function of and integration between frontal and striatal regions at multiple levels of organization contribute to a distinct adolescent brain (and subsequently behavioral) phenotype.

Dopamine

Frontostriatal circuits subserving affective, cognitive, and motor processes are significantly modulated by the neurotransmitter dopamine (DA) (for reviews see (Schultz 2002; Wise 2004; Cools 2008), through facilitation of the direct pathway via the action of excitatory DA receptors (D_1-like) and inhibition of the indirect pathway via the action of inhibitory DA receptors (D_2-like). DA neurons in the midbrain project to medium spiny neurons in the NAcc as well as pyramidal neurons in the PFC, thereby modulating the firing rates of these neurons and establishing a strong reciprocal relationship between striatum and PFC (Grace, Floresco et al. 2007). DA levels are modulated by two dissociable processes of DA discharge that interact, (1) a constant background tonicity regulated by baseline firing of DA neurons and glutamatergic afferents from cortical to striatal regions, and (2) a burst firing high-amplitude phasic release (Grace, Floresco et al. 2007). These two mechanisms of DA signaling have been found to lead to distinct behaviors (Floresco, West et al. 2003) and are regulated by reuptake and degradation enzymes. Fast phasic events occur in response to reward-related events, which may serve as important teaching signals for error detection and modulate behavioral changes in response to the environment (Schultz 1998). Slow changes in tonic levels of DA may be a preparatory mechanism for an organism to respond to environmental cues associated with reward (Schultz 1998). These systems also interact as tonic DA activity regulates phasic signaling in an inhibitory fashion and phasic DA has been shown to enhance tonic activity (Niv, Daw et al. 2007).

The DA system undergoes significant change over adolescence, which is relevant for adolescent behavior for several reasons. First, DA signaling supports reinforcement learning as it tunes the strength of synapses, thereby influencing plasticity. Second, DA modulation of striatal and prefrontal function influences affective and motivated behaviors that are altered in adolescence. Lastly, abnormalities in DA signaling are implicated in the pathophysiology of neuropsychiatric disorders that often emerge in adolescence (e.g. schizophrenia, drug abuse). The literature spanning the development of DA function and implications for adolescent behavior has been reviewed in depth elsewhere, (Spear 2000;

Chambers, Taylor et al. 2003; O'Donnell 2010; Wahlstrom, Collins et al. 2010; Wahlstrom, White et al. 2010; Luciana, Wahlstrom et al. 2012) and is summarized below. Much of the evidence on the DA system in adolescence is from non-human primate and rodent models and findings are not straightforward. 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 et al. 2009), suggesting an overall increase in DA levels. Other studies have noted a peak in tonic DA concentrations in late adolescence with a subsequent decline in adulthood ((Badanich, Adler et al. 2006; Philpot, Wecker et al. 2009). Non-human primate studies show that the highest concentrations of DA during adolescence are in the PFC before dropping down in adulthood (Goldman-Rakic and Brown 1982). In human post-mortem studies, DA levels in the striatum increase until adolescence and then decrease or remain the same (Haycock, Becker et al. 2003). In one study, extracellular levels of DA in the NAcc were lower in adolescence compared to adulthood (Cao, Lotfipour et al. 2007). Dopaminergic innervation to the PFC peaks in adolescence (Rosenberg and Lewis 1995; Benes, Taylor et al. 2000), with the largest increase being in cortical layer III, a region that that is highly implicated in cognitive processing (Lewis and Gonzalez-Burgos 2000). These changes occur both in length of individual axons and as well as total number of projecting axons (Rosenberg and Lewis 1994; Lambe, Krimer et al. 2000). There is also an increase in the density of synapses between DA neurons and pyramidal neurons in layer III of cortex (Lambe, Krimer et al. 2000) as well as a peak in glutamatergic connectivity from the PFC to the NAcc, specifically in D_1-expressing neurons (Brenhouse, Sonntag et al. 2008). Regarding receptor densities, non-human primate research suggests that the density of D_1 and D_2 receptors in PFC increase at different rates, with D_1 receptor density demonstrating earlier peaks than D_2, which peaks in late-adolescence/early adulthood (Tseng and O'Donnell 2007). A post mortem human research study found that D_1 receptor densities peak around 14–18 years of age (Weickert, Webster et al. 2007), declining thereafter. A peak in cells containing D_1 receptors in the PFC has also been documented (Andersen, Thompson et al. 2000; Weickert, Webster et al. 2007). 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 (Seeman, Bzowej et al. 1987; Lidow and Rakic 1992; Montague, Lawler et al. 1999; Andersen, Thompson et al. 2002). However, other evidence suggests that DA receptor densities decline in dorsal, but not ventral striatum (where levels remain the same) over adolescence (Teicher, Andersen et al. 1995). Research on DA transporters has been inconsistent in the midbrain suggesting no consistent developmental change (Moll, Mehnert et al. 2000), increases over adolescence (Galineau, Kodas et al. 2004), and peaks in late childhood (Coulter, Happe et al. 1996). Other research has suggested that in the striatum, DA transporter levels increase into late childhood and remain stable through adolescence (Coulter, Happe et al. 1996; Tarazi, Tomasini et al. 1998; Galineau, Kodas et al. 2004).

Adding to this complexity, maturational changes in DA function have not been mapped directly onto behaviors in adolescence suggesting that a comprehensive examination of the interaction of various aspects of the DA system (e.g. receptors, clearance, innervation) and their direct effects on behavior is warranted (Spear 2011; Luciana, Wahlstrom et al. 2012).

For example, the elevation of tonic DA during adolescence may impact regulation of the phasic response in response to salient or rewarding information (for review see (Luciana, Wahlstrom et al. 2012)), but this has not been empirically tested. It is posited that the DA system is at a "functional ceiling" in adolescence relative to childhood or adulthood (Chambers, Taylor et al. 2003), due to peaks in midbrain DA cell firing, overall tonic levels, innervation, as well as increased receptor densities. The adult literature suggests that increasing DA signaling through administration of DA or DA agonists increases novelty-seeking and exploration behaviors, whereas reducing DA signaling with antagonists halts such behaviors (Pijnenburg, Honig et al. 1976; Fouriezos, Hansson et al. 1978; Le Moal and Simon 1991). These early findings point to a hypothesized model of adolescent DA function whereby overall heightened DA signaling leads to heightened motivation, or approach-like behaviors-due to increased activation of the direct pathway and inhibition of the indirect pathway. Other evidence associating altered DA in adolescence to behavior suggest that adolescent rodents exhibit increased reinforcing effects to drugs that influence DA release, such as alcohol, nicotine, amphetamines, and cocaine (Adriani, Chiarotti et al. 1998; Laviola, Adriani et al. 1999; Adriani and Laviola 2000; Badanich, Adler et al. 2006; Shram, Funk et al. 2006; Frantz, O'Dell et al. 2007; Mathews and McCormick 2007; Brenhouse and Andersen 2008; Varlinskaya and Spear 2010). Adolescents also show decreased aversive response to substances of abuse (i.e. milder withdrawal responses, reduced psychomotor effects) (Spear 2002; Doremus, Brunell et al. 2003; Levin, Rezvani et al. 2003) and increased sensitivity to DA receptor antagonists (Spear, Shalaby et al. 1980; Spear and Brake 1983; Teicher, Barber et al. 1993). Research in adult human and animal models has suggested that intermediate levels of DA signaling in both PFC and striatum are necessary for optimal performance, following a Yerkes-Dodson inverted U-shaped dose response curve of DA signaling and behavior (Robbins and Arnsten 2009; Cools and D'Esposito 2011). Following this model, increased DA levels in adolescence may surpass the threshold required for optimal functioning (Wahlstrom, Collins et al. 2010; Wahlstrom, White et al. 2010). DA signaling in adolescence may also influence and be influenced by differences in rates of maturation of subcortical systems relative to cortical, and an functional imbalance in the adolescent brain that is driven by striatal signaling with immaturities in PFC-driven regulation (Chambers, Taylor et al. 2003; Ernst, Pine et al. 2006).

Despite an overall peak in DA signaling and general maturational processes that occur in adolescence, there is considerable individual variability both in DA signaling, as well as DA-influenced behaviors, likely due to a combination of genetic and environmental factors (Depue and Collins 1999; Frank and Hutchison 2009). Understanding the nature of these individual differences may have significant predictive power. For example, adolescents with higher levels of tonic DA levels, higher DA receptor densities, and lower rates of DA clearance and degradation may engage in DA-modulated behaviors (e.g. sensation/novelty seeking) to a larger extent than adolescents with decreased DA signaling and availability (For review see (Luciana, Wahlstrom et al. 2012)). These hypothesized patterns are based on prior adult studies that highlight the importance of the baseline state of the DA system – which varies across individuals. For example, increasing DA levels in individuals who have high baseline DA levels impairs cognitive performance, (perhaps pushing them over the peak of the inverted U curve) whereas improvements are noted in individuals with lower

baseline levels (pushing them closer to the apex of the curve) (Mattay, Goldberg et al. 2003; Apud, Mattay et al. 2007; Cools, Frank et al. 2009). While this model is simplistic, we use this as a framework to study the genetic factors that drive variability in DA function, and how these factors may interact with normative changes over development. Following this model, it is possible that baseline inter-individual differences in adolescence would be unique relative to differences in adulthood due to maturation in the DA system.

Developmental Imaging Genetics

Methodologically, characterizing the nature of neurochemical systems in human development is challenging, as pharmacological and other invasive procedures (i.e. PET) typically cannot be used to study developing populations. In an effort to develop biologically plausible and testable hypotheses on the influence of DA 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 brain function. Researchers have used functional and structural neuroimaging measures as intermediate phenotypes to better understand the influence of genetic variability on human behavior (Hariri and Weinberger 2003). This approach is grounded in the notion that genetic influences on behavior are mediated by changes in cellular and systems levels of functioning in the brain. Indeed, the study of the influence of genetic polymorphisms on brain function or "imaging genetics" has already provided considerable insight on the influence of genetically driven variability on brain physiology (e.g. (Hariri and Weinberger 2003; Brown and Hariri 2006; Drabant, Hariri et al. 2006; Hariri and Lewis 2006)). However see: (Flint and Munafo 2007; Walters and Owen 2007; Kendler and Neale 2010) for limitations and considerations of this approach. The rationale for 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. Given that the development of the DA system may affect some individuals more than others and that genetic effects are likely not static, and change across the lifespan, studying the influence of genetically-driven variability of the DA system on brain development has great potential to elucidate the biological basis of individual differences in behavior as well as risk for developing psychopathology.

Variants in genes that code for various DA-related proteins have previously been associated with inter-individual differences in frontostriatal brain function and structure (e.g. (Bertolino, Blasi et al. 2006; Drabant, Hariri et al. 2006; Yacubian, Sommer et al. 2007; Dreher, Kohn et al. 2009; Aarts, Roelofs et al. 2010), and with variability in behavioral phenotypes that are relevant to the study of adolescence including impulsivity, novelty seeking, aggressive traits, executive function, incentive processing, drug abuse, and the etiology of neuropsychiatric disorders such as schizophrenia, ADHD and Parkinson's disease ((Karayiorgou, Altemus et al. 1997; Eley, Lichtenstein et al. 2003; Enoch, Schuckit et al. 2003; Lee, Lahey et al. 2007), for review see (Nemoda, Szekely et al. 2011)). In the following sections we review neuroimaging studies of common functional polymorphisms in genes that influence DA signaling. We will discuss studies of both single nucleotide polymorphisms (SNP) and variable nucleotide tandem repeat (VNTR) polymorphisms. We focus specifically on imaging genetics studies using functional and structural magnetic

resonance imaging (MRI and fMRI). As evidence of behavioral associations with DA-related genes have been reviewed in depth elsewhere (e.g. (Nemoda, Szekely et al. 2011; Cormier, Muellner et al. 2013), we focus solely on imaging genetics research. Although this review is focused on normative development, we have summarized main findings of developmental imaging genetics research in both typical development and developmental disorders involving DA (such as schizophrenia and ADHD) in Table 1.

DA Receptor Genes (DRD1, DRD2, and DRD4)

The distribution of both D_1-(D_1 and D_5) and D_2 (D_2, D_3, D_4) -like receptors across the brain results in a complex balance of excitatory-inhibitory neuronal signaling, which exerts a strong influence on frontostriatal function and connectivity, with the largest density of receptors being in the striatum. Both D_1 and D_2-like receptors are G protein-coupled, and serve opposing roles, increasing and inhibiting cyclic adenosine monophosphate respectively, thereby exciting or inhibiting the activity of the neuron. D_1 and D_2 receptors thus have complementary roles. D_1 receptors stimulation allows for maintenance of information online and stabilization of functional states, and D_2 receptor binding is involved in flexible updating of information and allowing for the transition between functional states (Seamans, Durstewitz et al. 2001; Durstewitz and Seamans 2002; Seamans and Yang 2004). D_1 receptors are more abundant in the direct pathway, exciting GABAergic neurons in response to preferred behaviors, and D_2 in the indirect pathway, which inhibit GABAergic neurons and reduce the inhibitory effect of the indirect pathway. Increases in both D_1 and D_2 receptors, as seen in adolescence thus may have an overall excitatory effect on the brain, which could result in an increase in behaviors that are DA dependent (such as reward and novelty seeking).

In the PFC, D_1 receptors act on glutamatergic pyramidal cells, increasing task related firing (Farde, Halldin et al. 1987; Goldman-Rakic 1990; Lidow, Goldman-Rakic et al. 1991). Simultaneously, D_1 receptor activation on local GABAergic (inhibitory) interneurons serves to inhibit irrelevant glutamatergic inputs (Durstewitz, Seamans et al. 2000). Limited research has examined polymorphisms of the D_1-receptor gene (*DRD1*) in relation to brain structure/function. One study using adults demonstrated altered prefrontal-parietal functional connectivity during a working memory task in schizophrenic patients genotyped for the *DRD1* Dde I single nucleotide polymorphism consisting of an A to G substitution in the 50 UTR (Tura, Turner et al. 2008). AG heterozygotes, who have increased D_1 receptors, showed increased recruitment of DLPFC relative to AA homozygotes, who engaged a more widely distributed set of brain regions. These findings are in line with other work suggesting that increased prefrontal DA tone results in improved cognitive performance and more efficient prefrontal signaling (e.g. (Egan, Goldberg et al. 2001; Mattay, Goldberg et al. 2003)).

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 disinhib tion of inhibitory pathways (Cepeda and Levine 1998; Goto and 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, Grande et al. 2003). Decreased D_2 autoreceptor function increases DA release and individuals with decreased D_2-S demonstrate increased novelty-seeking and reward reactivity (Zald, Cowan et al. 2008; Pecina, Mickey et al. 2012). Functional polymorphisms in the gene that codes for the D_2 receptor (*DRD2*) that 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, Bertolino et al. 2007). Polymorphisms that influence D_2 binding include the DRD2/ANNK1 TaqIA, a restriction fragment length polymorphism that results in a Glu to Lys amino acid substitution in the neighboring ANNK1 gene, and the −141C Ins/Del SNP that is located in the promotor region of the DRD2 gene. The TaqI A1 allele and the Del allele have been associated with decreased striatal D2 binding (Arinami, Gao et al. 1997; Noble 2000), although one study suggests molecular heterosis with the TaqIA polymorphism, with decreased D_2 density in heterozygotes relative to homozygotes (Pohjalainen, Nagren et al. 1999). Thus, the Del and A1 alleles have been associated with increased reward reactivity in ventral striatum in adulthood (Cohen, Young et al. 2005; Forbes, Brown et al. 2009). The A1 allele has also been associated with decreased prefrontal activation and connectivity in frontostriatal circuits during task switching (Stelzel, Basten et al. 2010).

In contrast to the adult research, the few studies using only adolescent participants found that the A1 allele is associated with decreased reward reactivity in ventral (Stice and Dagher 2010) and dorsal (Stice, Spoor et al. 2008) striatum. In adolescence, when there is a higher density of D_2 receptors, the relationship between brain activation and D_2 receptor availability might parallel previous findings using pharmacological interventions that target D_2 receptors (Kirsch, Reuter et al. 2006; van der Schaaf, van Schouwenburg et al. 2012), suggesting an age by genotype interaction that is yet to be empirically tested.

The D_4 receptor is D_2-like and is expressed on both postsynaptic striatal neurons and pre-synaptic corticostriatal glutamatergic afferents. Limited evidence suggests that D_4 receptors develop similarly to D_2 receptors (with peaks in late childhood and subsequent declines into adulthood) (Tarazi, Tomasini et al. 1998). The gene (*DRD4)* that codes for the D_4 receptor has several functional polymorphisms, of which the 48-base pair VNTR in exon 3 that results most commonly in a 7-repeat or 4-repeat variant, is frequently studied. The 7-repeat allele is associated with decreased postsynaptic inhibition of DA, due to reduced cAMP-reduction potency, leading to a disinhibition of striatal neurons (Asghari, Sanyal et al. 1995; Seeger, Schloss et al. 2001), and has been associated with increased reward related reactivity in ventral striatum, relative to the 4-repeat allele (Schoots and Van Tol 2003; Forbes, Brown et al. 2009; Stice, Yokum et al. 2012). A SNP in the *DRD4* gene (rs6277, −521 SNP) results in a 40% reduction in RNA transcription for the T-allele relative to the C-allele (Okuyama, Ishiguro et al. 1999), although another study found no differences (Kereszturi, Kiraly et al. 2006). To date, one imaging study has reported that individuals homozygous for the C allele exhibit increased medial PFC/anterior cingulate activation during the processing of reward magnitude (Camara, Kramer et al. 2010). Only the DRD4 VNTR has been studied in developing populations, associating the 7-repeat allele reduced cortical thickness in the PFC of children (Shaw, Gornick et al. 2007), increased striatal activation to incentives in children

and adolescents as a moderator of anxiety in adolescents (Perez-Edgar, Hardee et al. 2013), and decreased activation to food rewards as a moderator of weight gain in adolescents (Stice, Yokum et al. 2010). The effects of this polymorphism on brain function in adolescence thus may parallel the adult findings.

Collectively, these studies demonstrate that functional variants in DA receptor genes influence frontostriatal brain function in children, adolescents and adults separately. However, no studies to date have examined the influence of these polymorphisms across development. Current research suggests that D_1 and D_2 receptor densities peak in late childhood, suggesting that receptor density is higher in adolescence relative to adulthood. Following the inverted U model, increased D_1 and D_2 receptor availability may result in increased competition between the direct and indirect pathways which may be more exacerbated in adolescents with higher receptor availability at baseline, leading to a generally more disorganized processing system.

DA inactivation genes (COMT, DAT1)

Functional Polymorphism in the *COMT* Gene

Catechol-O methyltransferase (COMT), an enzyme for catecholamine catabolism, is vital to regulating DA turnover in the PFC where DA transporters are scarce (Hong, Shu-Leong et al. 1998; Matsumoto, Weickert et al. 2003). Within the COMT gene (*COMT)* is a single nucleotide polymorphism (SNP) resulting in a methionine (*met*) to valine (*val*) substitution at codon 158 (Tunbridge 2010). The *COMT val* allele is associated with high enzymatic activity and consequently low synaptic dopamine levels, whereas the *COMT met* allele results in approximately one third less enzyme activity and consequently high synaptic dopamine (Chen, Lipska et al. 2004). Heterozygotes show intermediate levels of *COMT* activity. Despite being predominantly expressed in the PFC, the *COMT val158met* polymorphism is also associated with downstream effects on midbrain DA activity (Meyer-Lindenberg, Kohn et al. 2005).

The *COMT val158met* SNP has been widely studied in the context of frontostriatal activation during cognitive tasks (Egan, Goldberg et al. 2001; Bilder, Volavka et al. 2002; Malhotra, Kestler et al. 2002; Goldberg, Egan et al. 2003; Mattay, Goldberg et al. 2003; Diamond, Briand et al. 2004) including working memory, response inhibition, set shifting and reward processing. Evidence suggests that individuals with the *met* allele demonstrate more efficient cortical function (e.g.(Egan, Goldberg et al. 2001; Mattay, Goldberg et al. 2003; Meyer-Lindenberg, Kohn et al. 2005)) as well as reward-related increases in striatal activation (Yacubian, Sommer et al. 2007; Dreher, Kohn et al. 2009) relative to individuals with the *val* allele. Furthermore, increasing DA levels interacts with the *COMT val158met* SNP consistent with the putative inverted U model with *met* individuals demonstrating diminished cortical efficiency during tasks of cognitive control and *val* individuals demonstrating improvements (Mattay, Goldberg et al. 2003; Apud, Mattay et al. 2007). Based on this evidence, it is posited that adolescents, who have increased DA levels relative to adults, may follow a similar pattern as a function of *COMT* genotype as the pharmacological studies in adults. This is adolescents carrying the *met* allele may surpass optimal thresholds, which could result in less efficient cortical function, relative to *val*

(Wahlstrom, Collins et al. 2010; Wahlstrom, White et al. 2010). It is thus possible that inter-individual differences are expressed differentially as a function of relative DA across development based on genotype (e.g. the *val* allele may confer a relative advantage for cognitive function earlier in development, when DA levels are higher than in adulthood). However, limited research has examined the influence of the *COMT val158met* polymorphism in the adolescent brain, and these initial studies are mixed and require replication. During a visuo-spatial working memory task in individuals between the ages of 6 and 20,Dumontheil et al. (2011), demonstrated that activation in frontal and parietal regions increased across development in individuals homozygous for the *val* allele, but not *met* carriers, suggesting delayed development of cognitive function in individuals with the *val* allele. *Val/val* homozygotes also showed slower cortical thinning over development in posterior parietal cortex, perhaps reflecting slower pruning and relative inefficiency in cortical processing. *COMT* effects in adolescence have also been found in studies of structural and functional connectivity, with adolescents with the *val* allele showing increased white matter integrity and decreased resting brain perfusion relative to *met* (Thomason, Waugh et al. 2009; Thomason, Dougherty et al. 2010), although these studies weren't developmental with no adult comparison groups. Lastly, one lifespan study (ranging from 6–84 years) showed reduced gray matter volume in ventral PFC in *met/met* individuals relative to *val/val* but no age by genotype interactions (Williams, Gatt et al. 2008).

Functional Polymorphism in the *DAT1* Gene

The DA transporter (DAT) is mainly expressed in the striatum and is responsible for DA reuptake, clearing DA from the extracellular space after release (Jaber, Bloch et al. 1998). A VNTR polymorphism in the gene that codes for DAT (*DAT1* or *SLC6A3*) results in alleles between 3 and 13 repeats of a 40-base pair sequence in its 3' untranslated region (Vandenbergh, Persico et al. 1992) as coding region variants are quite rare. The DAT binding site density for the most common repeat alleles (9-repeat and 10-repeat) is significantly less for the 9-repeat allele than the 10-repeat allele, linking the 9-repeat allele with reduced DAT expression and greater striatal synaptic DA (Fuke, Suo et al. 2001; Mill, Asherson et al. 2002; VanNess, Owens et al. 2005), although some studies have suggested the opposite (Mill, Asherson et al. 2002; van de Giessen, de Win et al. 2009). Lower DAT expression reduces synaptic DA clearance thereby increasing DA levels (Cagniard, Balsam et al. 2006; Cagniard, Beeler et al. 2006). FMRI research most consistently associates the 9R allele with increased reward reactivity in the striatum (Yacubian, Sommer et al. 2007; Dreher, Kohn et al. 2009; Forbes, Brown et al. 2009). Although DAT is primarily expressed in striatum, evidence associates the 9-repeat allele with increased ventral striatal and dorsomedial PFC activation during working memory updating and task switching (Aarts, Roelofs et al. 2010; Garcia-Garcia, Barcelo et al. 2010), and increased PFC activation during inhibitory control, which was interpreted as supporting improved inhibitory control (Congdon, Lesch et al. 2008; Congdon, Constable et al. 2009). Developmental studies using the *DAT1* polymorphism suggest that typically developing adolescents with the 9-repeat allele demonstrate reduced activation of prefrontal and striatal regions during inhibitory control (Braet, Johnson et al. 2011), and reward prediction (Paloyelis, Mehta et al. 2012). These results suggest that DAT1 genotype may influence the system differentially in adolescence – with the 9-repeat allele resulting in decreased striatal and cortical reactivity-

than in adulthood – when the 9-repeat allele has been associated with increased activation. It is possible that in adolescence, when excess DA levels are present, individuals carrying the 9-repeat allele have an overabundance of synaptic DA availability, which may have opposite effects on brain function than in adulthood.

Gene-Gene Interactions

Imaging genetics research has predominantly focused on single functional polymorphisms in candidate genes. The complexity of the DA system, the differing rates of maturation of various aspects of the system, the interactions of the various components of the system, and the interaction of the DA system with other brain processes, suggests that gene effects are likely not independent or dichotomous. Investigators have more recently started to study interactions between or cumulative effects of multiple genes. Given evidence that various aspects of the DA system are heightened or changed in adolescence and that single gene effects may manifest differently in the adolescent brain, it is also possible that gene interactions differ in the adolescent brain than in the adult brain. Assuming equal effect sizes of each polymorphism, prior studies have demonstrated effects on brain activation as a function of interactions between genes (Bertolino, Blasi et al. 2006; Yacubian, Sommer et al. 2007; Bertolino, Di et al. 2008; Dreher, Kohn et al. 2009). For example, prior studies have shown additive effects of the *COMT val158met* SNP and the *DAT1* 3'VNTR during the reward anticipation and outcome stages of reward processing in both PFC and striatum, reporting increased activation associated with genotypes that have increased DA availability (Yacubian, Sommer et al. 2007; Dreher, Kohn et al. 2009). However, due to limited sample sizes, these studies have only examined two polymorphisms as once. More recently, researchers have explored the influence of several DA genes on brain function during reward processing using a "multilocus composite score" (Plomin, Haworth et al. 2009), assigning each participant a single additive score based on relative levels of DA signaling. The idea behind this approach is that combining multiple functionally relevant genes through a cumulative profile score may explain more variability than single loci that may independently have non-significant effects. This research combining COMT, DAT1, and DA receptor genotypes has shown increased ventral striatal reactivity as a function of increasing DA signaling in adulthood (Nikolova, Ferrell et al. 2011), and caudate and putamen in adolescence (Stice, Yokum et al. 2012) during receipt of monetary rewards. Replication of these findings, and exploration of gene interactions over development is necessary in order to better understand cumulative effects of genotype.

Considerations and Future Directions for Imaging Genetics studies

The genetic basis for complex behavioral traits is likely a result of allelic variation across many genes/polymorphisms and their interactions with each other and the environment. The majority of imaging genetics research has focused on associations between brain function and single or a handful of genes or polymorphisms. In addition, because neuroimaging studies require relatively evenly distributed groups, imaging genetics research is predominantly focused on high frequency alleles that are evenly distributed in the population thus having favorable or neutral effects. The downside to this approach is that these variants only explain only a small proportion of the variance in complex disorders or

traits. Therefore, the main purpose of imaging genetics is not to find causal genetic links, but to better understand the neural underpinnings of complex behaviors.

Since single genetic polymorphisms have very small effects on multidimensional and heterogeneous behaviors and traits, the study of the influence of common variants on brain function requires maximal sensitivity and reliability of the measures obtained. Imaging genetics studies should utilize well-defined and objectively measured phenotypes of interest (i.e. fMRI tasks used must reliably and robustly engage circumscribed brain systems and demonstrate variance across participants). fMRI is one the most common and reliable methods of measuring brain function at decent spatial and temporal resolutions, but given that it is an indirect measure of brain activity, reflecting a paradigm related change in metabolic consumption (Logothetis, Pauls et al. 2001), interpretation of gene effects is limited. Thus, combining multimodal approaches that measure brain function and structure at varying spatial and temporal resolutions and creating adequate measures of environmental factors would be beneficial for further understanding genetic effects on brain function (Bigos and Hariri 2007; Fisher, Munoz et al. 2008; Nemoda, Szekely et al. 2011). Genetics research would also benefit from translational work, studying the influence of candidate genes in both humans and genetically modified animal models using similar behavioral/ neurofunctional phenotypes (Casey, Soliman et al. 2010). Despite the limitations of translating human behavior to animals, studies using genetically modified mouse models for key DA genes, including *COMT* and *DA* receptor genes have demonstrated similar cognitive and behavioral effects similarly to humans (for review see (Casey, Soliman et al. 2010)). Thus, it is possible that gene effects on the brain would also show important similarities across species. Furthermore, developmental animal models have the advantage of shorter lifespans and stricter control of the environment.

Another way to improve reliability in imaging research is to use sample sizes that afford the power to detect small to medium effects. Initial reports have suggested that the relative proximity of brain function to the genotype may permit gene effects to be observed in fewer participants than typical behavioral studies. For example, Munafo et al. (2008) conducted a meta-analysis of studies that have reported associations between a VNTR polymorphism in the serotonin transporter gene (*5-HTTLPR*) and amygdala activation and suggested that an imaging genetics study would require a total sample of about 70 participants to achieve .8 power for an alpha power of .05. Assuming a relatively even distribution of the alleles, this would result in approximately 30–35 participants per group. Similarly, others have suggested that sample sizes of over 25 subjects in each group are necessary for general fMRI studies in order to have adequate reliability (Thirion, Pinel et al. 2007). Meta-analyses to determine effect sizes of previous imaging genetics studies and ideal sample sizes for future ones is warranted for studies of DA-gene polymorphisms (Munafo, Bowes et al. 2005; Barnett, Scoriels et al. 2008). However, it is also important to keep in mind that meta-analyses tend to be biased, as studies with null findings are generally not published. It is likely that sample sizes will have to be increased in order to replicate previous findings and to generate accurate assessments of the effect sizes of different polymorphisms.

Summary/Conclusions

The inability to consistently control behavior concurrent with increased sensation seeking persists in adolescence, leading to increases in risk taking behaviors. Although these behaviors may be mediated by non-biological factors, we must characterize the biological mechanisms driving development in order to better understand their consequences. Evidence points to a protracted development of brain systems including PFC and the striatum throughout childhood and adolescence. These systems support motivationally driven behaviors and may contribute to vulnerabilities in the emergence of psychopathology. The PFC and striatum support incentive driven behaviors through their unique interconnectivity, which is modulated by the function of DA. DA availability and signaling is heightened during the adolescent period and may promote novelty seeking in an adaptive fashion in order to gain skills that support adult survival. However, 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, thereby increasing vulnerability for risk-taking behaviors. Despite general patterns of maturational change in DA, there is great variability in adolescent behaviors, which generates questions about the biological mechanisms that underlie this variability, a line of research yet to be explored. Gene expression is one of the primary sources of variability, acting through cellular and system-level neural processes to produce complex phenomena that manifest in behavioral function and dysfunction. The majority of imaging genetics research to date has focused on differences between genotypes in adulthood or within discrete age groups, despite growing evidence that brain systems continue to reorganize across the lifespan and that gene effects likely manifest differently at different stages. Identifying the nature of these changing trajectories will be more informative to the study of the brain than measuring static differences within age groups. The limited developmental imaging genetics research (i.e. (Dumontheil, Roggeman et al. 2011) has suggested that the direction of gene effects on brain function may change over development as brain systems reorganize. Future imaging genetics work should study gene effects across development (and the life span), ideally in a longitudinal fashion. This can have strong implications for understanding the neurobiology of heightened risk taking during adolescence, recognizing vulnerabilities for the emergence of psychopathology, developing age specific treatments, and the identifying the individual pathways that lead to behavioral outcomes in adulthood.

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Highlights

- Frontostriatal systems underlying motivated behaviors are immature in adolescence

- The dopamine system undergoes significant reorganization over adolescence

- Imaging genetics can be used to study the biological basis of variability in brain function

- Imaging genetics may be valuable to study the influence of dopamine in adolescence

Reference	Gene/s	Population	Methodology	Main Findings
Durston et al., (2008)	DAT1 3'VNTR	10 ADHD, 9R = 4, 10R/10R = 6; 10 Unaffected siblings, 9R = 5, 10R/10R = 5; Controls, 4 9R, 5 10R/10R = 5, all male, aged 11–20	Go/No-Go inhibitory control paradigm (fMRI)	Striatal activation was increased in 9R carriers relative to 10R/10R homozygotes. 10R/10R showed increased activity in cerebellar vermis. Genotype by diagnosis interaction suggested that 9R ADHD and sibling groups showed increased activity in striatum relative to controls and 10R/10R counterparts.
Braet et al., (2011)	DAT1 3'VNTR	20 ADHD (aged 14.1 +/− 2.1), 17 males, 11 9R, 9 10R/10R; 38 Controls (aged 13.26 +/− 1.98), 31 males, 20 9R, 18 10R/10R	Sustained attention to response task (SART) - go/no-go inhibitory control paradigm (fMRI)	Diagnosis by genotype interactions suggested that ADHD participants homozygous for the 10R allele showed increased activation in frontal, medial, and parietal regions and reduced error response in para hippocampus gyrus; frontal, parietal, medial, and occipital regions relative to ADHD 9R carriers. There were no brain activation differences between 10R/10R and 9R TD participants.
Bedard et al., (2010)	DAT1 3'VNTR	33 ADHD (aged 7–16), 24 males, 12 9R, 21 10R/10R	Go/No-Go inhibitory control paradigm (fMRI)	Participants homozygous for the 10R allele had significantly greater inhibitory control-related activation than 9R carriers in the left striatum, right dorsal premotor cortex, and bilaterally in temporoparietal cortical junction
Raznahan et al., (2011)	COMT Val158Met SNP	83 Childhood Onset Schizoprhenia (COS), 48 males, 12 met/met, 42 val/met 62 val/val; 62 Siblings, 32 males, 13 met/met, 30 val/met, 19 val/val; 208 Controls, 118 males, 60 met/met, 91 val/met, 57 val/val, aged 9–22	Structural (MRI)	Increasing number of val alleles accelerated cortical thinning across development in proband and sibling groups, but attenuated cortical thinning in healthy controls.
Perez-Edgar et al., (2013)	DRD4 48-bp VNTR	78 Anxiety disorder (aged 16.33 +/− 2.84), 38 males, 34 7R+, 46 7R−	Monetary incentive delay (MID) task and behavioral inhibition (BI) measure (fMRI)	DRD4 status moderated the relation between BI and activation in caudate nucleus, with 7R+ individuals showing modulation of activation by incentive cue and 7R− showing change by incentive cue.
Stice et al., (2012)	TaqIA SNP, DRD2-141C Ins/Ins SNP, DRD4 48 bp VNTR, DAT1 3' VNTR, COMT Val158Met SNP, multilocus composite score	160 Typically Developing (aged 15.3 +/− 1.07), 79 males	Reward task (food reward) (fMRI)	Lower DA signaling as computed by a multilocus composite score was correlated with increased activation in putamen, caudate and insula during reward receipt.
Stice et al., (2010)	DRD2 TaqIA SNP, DRD4 48-bp VNTR	39 Typically Developing (aged 15.6 +/− 0.96), 0 males, 13 DRD2 A1+, 19 DRD2 A1−, 11 DRD4-7R +, 21 DRD4-7R−	Reward task (imagined intake of palatable foods, unpalatable foods, & water) (fMRI)	Individuals with DRD2-A1 and DRD4-7R showed weaker activation of reward circuitry including frontal operculum, lateral OFC and striatum, which predicted future increases in body mass. Individuals without the DRD2-A1 and DRD4-7R alleles showed increased activation of these same regions, which also predicted future increases in body mass.
Stice et al., (2008)	DRD2 Taq1A SNP	27 Typically Developing (aged 15.7+/−1.02), 0 males, 10 DRD2 A1+, 17 DRD2-A2+	Reward task (food reward) (fMRI)	DRD2 genotype moderated the relationship between BOLD activation in striatum during reward receipt and body mass index and future weight gain, where individuals with the A1 allele showed a negative correlation between BOLD and BMI and individuals without

Reference	Gene/s	Population	Methodology	Main Findings
				the A1 allele showed a positive correlation.
Thomason et al., (2010)	COMT Val158Met SNP	40 Typically Developing (aged 9–15), 14 males, 6 met/met, 21 val/met, 13 val/val	Diffusion tensor imaging (fMRI)	Individuals homozygous for the val allele showed increased FA in the corpus callosum, anterior thalamic radiation, and uncinate fasciculus relative to heterozygotes and met/met.
Thomason et al., (2009)	COMT Val158Met SNP	44 Typically Developing (aged 9–16), 14 males, 6 met/met, 23 val/met, 13 val/val	Resting brain perfusion (arterial spin labeling)	Met/Met homozygotes exhibited greater resting regional cerebral blood flow in midbrain, dACC, Nacc, medial, and lateral PFC, dorsal striatum, and insula relative to val carriers
Williams et al., (2008)	COMT Val158Met SNP, DRD4 48bp VNTR	276 Typically Developing (aged 6–84), 148 males	Structural (MRI)	Main effect of genotype for the *COMT* polymorphism. Met/Met individuals showed reduced gray matter volume relative to val/val in VMPFC and VLPFC. No age by genotype interactions
Gilsbach et al., (2012)	DRD4 48-bp VNTR	26 Typically Developing (aged 8–16), 17 males, 7-repeat-abscent = 16, 10 males; 7-repeat-present = 10, 7 males	Combined stimulus-response Incompatibility (IC) and Time Discrimination (TT) executive function tasks (fMRI)	7-repeat-abscent individuals showed increased activation of left and middle inferior frontal gyrus during IC task increased cerebellar activation during TT task. 7-repeat-abscent individuals also showed stronger connectivity between left IFG and ACC during IC and between cerebellum and ACC and rIFG during TT task.
Mechelli et al., (2009)	COMT Val1 58Met SNP	50 Typically Developing (aged 10–12) 50 males, 14 met/met, 22 val/met, 14 val/val	Presentation of emotional and neutral faces (fMRI), Structural (MRI)	Linear effect of COMT met allele on gray matter volume in left hippocampal head. Met allele was also positively associated with BOLD response to fearful versus neutral faces in right parahippocampal gyrus and increased functional coupling as a function of increasing met alleles between the parahippocampal gyrus and the anterior cingulate cortex.
Dumontheil et al., (2011)	COMT Val158Met SNP	81 Typically Developing (aged 6–20) Val/Val N = 21, Met carriers N = 60	Dot matrix working memory paradigm (fMRI) and VBM (MRI)	Val/Val homozygotes showed increased working memory related activation and decreased gray matter volume over age in intraparietal sulcus, Met carriers showed no developmental change.