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Special Invited Review

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 non-invasively 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.

Contents

1. 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 & Tanner, 1986; Romeo, 2003). These biological changes

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reciprocally interact with the environment and characterize 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 (Chambers, Taylor, et al., 2003; Paus, Keshavan, et al., 2008; Pine, 2002; Sisk & Zehr, 2005), 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 in rational behaviors (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 (Blakemore & Robbins, 2012; Casey, Getz, et al., 2008), 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 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 & 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.

2. Incentive driven behaviors and frontostriatal circuits in adolescence

Evidence suggests that adolescents tend to both process incentives differently than adults (for reviews see Ernst, Daniele, et al., 2011; Geier and Luna, 2009), 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 et al., 2008; Ernst & Fudge, 2009).

The human striatum is recognized as a core node for incentive-driven behaviors, including 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; Di Martino, Scheres, et al., 2008; Postuma & Dagher, 2006) that underlie distinct behaviors (Tekin & 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 (NAcc)) 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. 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 (Casey et al., 2008; Ernst, Pine, et al., 2006; Nelson, Leibenluft, et al., 2005, for a summary of these models see Sturman & 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; Bjork, Smith, et al., 2010; Ernst, Nelson, Leibenluft, et al., 2005; Galvan, Hare, et al., 2006; Padmanabhan, 2011; van Leijenhorst & Moor, 2010), 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; Fair, Cohen, et al., 2009; Hwang, Velanova, et al., 2010; Liston, Watts, et al., 2006; Stevens, Pearlson, et al., 2009). Animal and post-mortem human literature suggests an overexpression of receptors for serotonin, dopamine, adenergic, and endocannabinoids (Lidow & Rakic, 1992), a peak in the density of interneurons (Anderson, Classey, et al., 1995; Erickson & Lewis, 2002; Lewis, 1997), 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 (Andersen, 2003; Benes, Turtle, et al., 1994; Rakic, Bourgeois, et al., 1986; Yakovlev & Lecours, 1967) refine the developing brain and strengthen and consolidate highly used connections, while weakening or eliminating redundant or weakly used connections through unique experiences (Giedd,