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Review

Evidence for a role of corticopetal, noradrenergic systems in the development of executive function

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ABSTRACT

Adolescence is a period during which many aspects of executive function are maturing. Much of the literature has focused on discrepancies between sub-cortical and cortical development that is hypothesized to lead to over-processing of reinforcement related stimuli unchecked by fully matured response inhibition. Specifically, maturation of sub-cortical dopaminergic systems that terminate in the nucleus accumbens has been suggested to occur prior to the full maturation of corticopetal dopaminergic systems. However, converging evidence supports the hypothesis that many aspects of cognitive control are critically linked to cortical noradrenergic systems, that the effectiveness of drugs used to treat disorders of executive function, e.g. ADHD, may result primarily from increases in cortical norepinephrine (NE) and that cortical noradrenergic systems mature across adolescence. However, little attention has been given to the development of this system during adolescence or to its influence in executive function. In the present paper, we discuss the developmental trajectory of the noradrenergic system of the forebrain, highlight the interactions between noradrenergic and dopaminergic systems, and highlight the contribution of the immature corticopetal noradrenergic systems in the ontogeny of several aspects of executive function. Finally we compare data from adolescent rats to those gathered after selective depletion of NE in sub-regions of the prefrontal cortex with an emphasis on the similarities in performance of NE lesioned rats and adolescents.

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1. Introduction

The developmental period of adolescence is a critical time of social, cognitive and emotional maturation. While diagnosis of attention deficit and anxiety disorders often occurs at an early age, there is a marked increase in the prevalence of mental disorders starting in adolescence (Merikangas et al., 2010). A prominent framework posits that immaturities in cognitive control result from disparate rates of maturation between sub-cortical structures and the prefrontal cortex (Casey & Jones, 2010; Mills, Goddings, Clasen, Giedd, & Blakemore, 2013). Specifically, the development

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of the prefrontal cortex shows that during adolescence white matter continues to mature, but fiber tracts decrease well into late adolescence and early adulthood (Giedd et al., 1999). This discrepancy in maturation between cortical and sub-cortical regions is hypothesized to produce adult-like processing of reinforcement in the absence of fully matured response inhibition contributing to poor impulse control and increased vulnerability to addiction during adolescence (Casey & Jones, 2010).

While there can be disagreement among investigators about the exact nature of the immaturity, these frameworks share in common a focus on the dopaminergic system with a great deal of research aimed at understanding the interaction of projections arising from the ventral tegmental area, which terminate in the prefrontal cortex and various cortical sub-regions, e.g. the nucleus accumbens. Converging evidence supports the translational utility of rat models to capture brain development during adolescence demonstrating parallel changes in dopaminergic systems of rats and humans between adolescence and adulthood. From postnatal day (PND) 25 to 40 corresponding to juvenile and young adolescent stages of development, studies of rats have shown that maturation of sub-cortical dopaminergic systems varies across terminal regions. D2 dopamine (DA) receptor levels in the striatum, nucleus accumbens and prefrontal cortex increase from PND 20 to 40. These same receptors decrease in the striatum and accumbens from PND 40 to 60. There is more protracted period of pruning in the prefrontal cortex of D2 receptors with the nadir occurring at PND 100, hypothesized to be roughly equivalent to human development in the early 20s (Andersen, Thompson, Rutstein, Hostetter, & Teicher, 2000). These differences in maturation of the mesolimbic and mesocortical DA systems, and the slowed development of the descending glutamatergic cortical inhibition of the nucleus accumbens are often cited as the reason for the increase in risky behavior and substance abuse in adolescence (O'Dell, 2009).

Behavioral assessments of the sensitivity to reward processing in rats seem to support heightened reward processing in adolescent rats akin to that shown in humans as a result of developmental changes in dopaminergic systems. Adolescent rats are slower to learn reward response contingencies have been reversed (Newman & McGaughy, 2011a). Adolescents are also less sensitive to both extinction (Andrzejewski et al., 2011), and reward devaluation than adults. Together these findings support the hypothesis that adolescent rats like humans are more sensitive to rewarding stimuli than adults (Hammerslag & Gulley, 2014). This emphasis on dopaminergic development has been justified by the mechanism of action of drugs used to treat disorders common during development such as attention deficit hyperactivity disorder (ADHD) as well as the role of DA in mediating many aspects of cognitive control that are developing during this period (Dalley, Cardinal, & Robbins, 2004).

However, studies confirm many aspects of executive function are critically linked to cortical noradrenergic systems (Bari & Robbins, 2013; Dalley et al., 2004; Lapiz & Morilak, 2006; McGaughy, Ross, & Eichenbaum, 2008), that effective doses of medications used to treat ADHD may result primarily from increases in cortical NE (Spencer, Devilbiss, & Berridge, 2015) and that cortical noradrenergic systems are fundamentally different between adolescents and adults (Bradshaw, Agster, Waterhouse, & McGaughy, 2016; Staiti et al., 2011). For example, atomoxetine, tradename Strattera, is a selective norepinephrine reuptake inhibitor that is effective in treating ADHD in adults (Chamberlain et al., 2007), adolescents and children (Wietecha et al., 2013). Moreover, cortical NE has been consistently linked to vulnerability to stress, and known to exacerbate several neuropsychiatric disorders. Surprisingly, there is little known about the developmental trajectory of this system. As a result of this gap in the literature, we will focus on the often understudied corticopetal noradrenergic systems to highlight how these systems are changing over the course of adolescence and to link these changes to the development of executive function during this period. In addition, we will discuss what is known about the interactions between noradrenergic and dopaminergic systems of the forebrain.

2. Development and interactions between noradrenergic and dopaminergic forebrain systems

As we have noted above, DA and NE are key neurotransmitters regulating cognitive processes in the prefrontal cortex. As we discuss development of cognition, the timing of these systems is critical to understanding the milestones of development. Norepinephrine modulates activity of dopaminergic cells in the ventral tegmental (VTA), the origin of both the mesolimbic and mesocortical pathways implicated in reward processing and other aspects of cognition. Stimulation of NE receptors by peripheral *in vivo* drug administration in the VTA increase firing rates. Furthermore, NET inhibition also increases firing rate and NE antagonists at alpha 1 and beta 2 receptors decrease firing rates (Mejias-Aponte, 2016). This complex system needs to be considered in addition to the developmental differences in assessing control of cognitive functions in the PFC as well as the mesolimbic pathway.

In adults, both NE and DA act on pyramidal cells in the cortex to modulate working memory. Too little DA or NE will decrease performance on working memory tasks (Xing, Li, & Gao, 2016). Furthermore, too much DA or NE will also cause a decrease in performance. Thus, both DA and NE have inverted U response curves. Optimal functioning of the prefrontal cortex is hypothesized to require activation of DA D1 receptors and adrenergic α2A receptors. Indeed, guanfacine, an α2A-AR agonist is being used clinically for a number of PFC related cognitive disorders including ADHD in children (Arnsten & Wang, 2016). To further complicate matters, DA is a substrate for the NE transporter (NET) and is taken up into noradrenergic neurons. Furthermore, it has been shown that NE neurons are capable of releasing DA (Mejias-Aponte, 2016). If this is the case it could would appear that NET is a primary site of regulation of both NE and DA in the PFC. This make explain the efficacy of the selective NE reuptake inhibitor, atomoxetine, which increases both cortical NE and DA at higher doses (Tzavara et al., 2006). These effects need to be compared to those of MPH and amphetamines, which are releasers as well as reuptake inhibitors.

Anatomical studies of the developing cortex in rats using the precursor to NE, dopamine β hydroxylase (DBH) to elucidate axons has shown that sensory and motor regions of the cortex mature around PND 15 in the rat (Latsari, Dori, Antonopoulos, Chiotelli, & Dinopoulos, 2002) with frontal regions becoming adult-like by PND 16 (Levitt & Moore, 1979). In contrast, classic studies of the dopaminergic systems show they mature later, possibly not becoming totally mature until early adulthood. Our lab (JM) completed immunohistochemical studies of DBH and the norepinephrine transporter (NET) between adolescence and young adulthood in rats (PND 40, 50, and 60). We found that while DBH was relatively stable across these ages, NET was changing (Bradshaw et al., 2016). Moreover, these changes in NET varied based on the sub-region of prefrontal cortex assayed. The anterior cingulate cortex (ACC), infralimbic (IL) and medial orbitofrontal (MOrb) showed no changes in NET density between PND 40 and 60. In contrast, NET density in the prelimbic cortex (PL) declined in a linear fashion between PND 40 and 60 while lateral orbitofrontal cortex (LOrb) showed a steep decline between PND 40 and 50 but was unchanged between PND 50 and 60. We hypothesize that the higher density of NET in the