The adolescent brain : unraveling the neural mechanisms of cognitive and affective development

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Chapter 1

General Introduction

Adolescence

Adolescence is an important developmental stage marking the transition from childhood to adulthood. The exact time period of adolescence is not well-defined, but it is generally thought to begin with the onset of puberty (around age 9-12 years; Marshall & Tanner, 1969, 1970). Puberty is characterized by a sudden surge in sex hormones, most markedly the hormone testosterone for boys and estradiol for girls. This surge in hormones is associated with the development of secondary sex characteristics, such as body hair growth and voice lowering for boys, and breast development and the first menstruation for girls (Petersen, Crockett, Richards, & Boxer, 1988). The end of adolescence, i.e. the entering of 'adulthood', is less clear and seems to be mostly culturally defined. For instance, in Western cultures adulthood is generally thought to begin when a child becomes relatively independent from parents (Choudhury, 2010).

Aside from drastic changes in physical characteristics, adolescence is also known as a period of marked behavioral changes. During adolescence, there is a gradual development of cognitive control or 'executive functions', i.e., the ability to control and regulate one's own actions, but at the same time, adolescents show increased sensitivity to affective and social rewards (Galvan, 2013). For instance, adolescents are prone to increased impulsivity and risk taking behaviors, such as substance use, reckless driving, unprotected sex, and violent behaviors (Steinberg et al., 2008). Health-risk behaviors are the leading cause of mortality amongst persons 10-24 years old in the United States (Kann et al., 2014; Sells & Blum, 1996). The increased incidence of risk taking in adolescence and the associated heightened mortality rate is a problem for society, and a growing amount of research attention is directed towards the mechanisms behind cognitive control and risk taking in adolescence. The goal of this thesis was to investigate both cognitive and affective aspects of development in adolescence, combining the use of neuroimaging methods, behavioral measures and hormonal assessments.

Brain development in adolescence

An increasing amount of research on adolescent cognitive control and risk taking has focused on the dynamic changes in brain development during this period. One of the main methods to examine brain development is by using magnetic resonance imaging (MRI). With MRI scanners, it is possible to create images of an individuals' brain in a safe and noninvasive manner, thus making it suitable for investigating healthy and underage participants. Although MRI provides images of the structure of the brain, the emergence of functional MRI (fMRI) has ensured that we can also study the functioning of the brain, i.e. which brain areas are engaged while performing a certain task. In addition, functional connectivity between regions can for instance be studied using resting state fMRI, to determine which regions are interconnected when a person is at rest.

Several key studies have shown that the brain continues to develop for a longer period than previously thought, with structural development continuing until around the early twenties (Giedd, 2004; Koolschijn & Crone, 2013). Structural brain development has been studied in both

gray matter (the brain cells, i.e. neurons) and white matter (the connections between neurons). Research has shown that white matter increases in a roughly linear fashion between childhood and adulthood (Giedd, 2004; Giorgio et al., 2010). Gray matter, on the other hand, follows an inverse U-shaped developmental trajectory, with cortical thickness increasing in childhood and decreasing in adolescence until the levels stabilize in adulthood (Giedd, 2004; Gogtay et al., 2004; Tamnes et al., 2010). Importantly, the development of gray matter does not occur at the same speed in each brain region. Development appears to be slowest in the prefrontal and parietal cortex (Giedd et al., 2009), the regions that are especially associated with cognitive control functions (Diamond, 2013; Niendam et al., 2012).

Models of brain development in adolescence

The results from these neuroimaging studies have been used to explain both the increasing capacity for cognitive control from childhood to adulthood, as well as the adolescent-specific rise in risk taking. These and other studies have led to the formulation of models for brain development that attempted to explain the increased incidence of risk taking behavior in adolescence. These models (e.g. Ernst, Pine, & Hardin, 2006; Somerville & Casey, 2010; Steinberg, 2008) have used different names but here I used the term 'imbalance models' of adolescent development (see Figure 1).

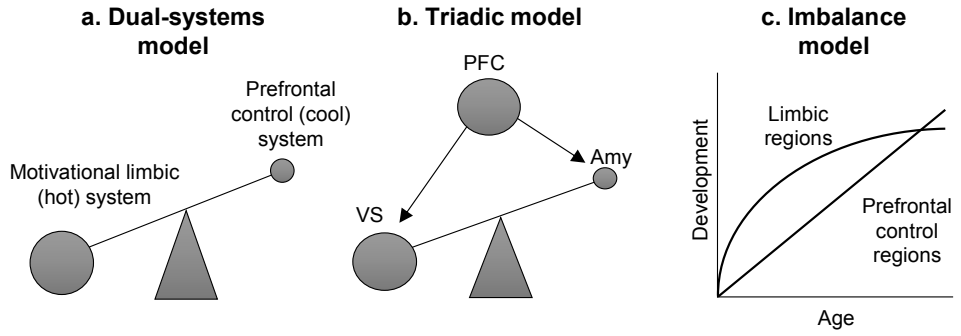

Figure 1: Adapted from Casey et al. (2015). Models of adolescent brain development. Abbreviations: Amy = amygdala, PFC = prefrontal cortex, VS = ventral striatum

The models are based on the findings that structural brain development in 'cognitive' regions (e.g. frontal and parietal cortex) is relatively delayed compared to 'affective' brain regions (e.g. striatum, amygdala). Specifically, it appears that affective brain regions mature relatively quickly, with some studies showing an adolescent peak in activity (Braams, Peters, Peper, Güroğlu, & Crone, 2014; Braams, van Duijvenvoorde, Peper, & Crone, 2015; Galvan et al., 2006; Van Leijenhorst et al., 2010). Cognitive brain regions in the frontal and parietal cortex on the other

hand, develop relatively more slowly with a gradual increase throughout adolescence. The hypothesis in imbalance models is that in adolescence, cognitive regions are not mature enough to keep relatively mature or even hyperactive affective regions under control, leading to increased risk taking behaviors. Naturally, this is a simplified account of brain development, but an intuitively appealing account that has inspired numerous other studies.

Towards new models of adolescent brain development

More recently, several authors (Casey, 2015; Crone & Dahl, 2012; Johnson, 2011; Pfeifer & Allen, 2012) have voiced the need for adjustments to imbalance accounts of adolescent development. One of the main reasons for this was that findings on development of functional brain activity were not always consistent with an imbalance model of adolescent development. For instance, although many studies found an increase with age in activity in the prefrontal cortex during cognitive tasks (as predicted by imbalance models), numerous studies also reported decreases in activity with increasing age. Both increases and decreases in activity with advancing age have been interpreted as reflecting increasing maturity (Pfeifer & Allen, 2012). That is, decreased activity in children and adolescents relative to adults has been interpreted as reflecting the immaturity of underlying brain structure and/or an inability to recruit these regions, whereas the studies showing increased activity in children and adolescents interpreted this as possibly less efficient and less focal activity compared to adults. It is a problem that this makes imbalance models virtually unfalsifiable (Pfeifer & Allen, 2012). In addition, many prior studies have collapsed across age groups (e.g. 8-12, 13-17 years), which increases power but decreases sensitivity to pinpoint exact moments of change, and very few studies have attempted to disentangle whether neural changes with development can be ascribed to age, or rather to differences in task performance or strategy use.

Other authors therefore argued instead for a different model emphasizing an increased flexibility of recruitment of control regions in adolescence, depending on motivational salience (Crone & Dahl, 2012). In other words, the hypothesis is that children and adolescents are in fact capable of recruiting brain regions for cognitive control, but often under different circumstances than adults. For instance, when motivation for a certain task is high (e.g., learning to play a new computer game, planning a birthday party), frontoparietal regions can be recruited by adolescents, and under very salient circumstances possibly even more strongly than in adults. Support for the idea that frontoparietal recruitment is not only a matter of increasing age comes from several sources. First, studies on relatively complex forms of executive functions such as performance monitoring paradigms, which rely on multiple executive functions such as working memory, inhibition and switching, have shown that the frontoparietal network is not exactly 'offline' in younger children. Instead, it appears that this network is activated in different situations for children than in adults. That is, in a task in which participants are instructed to learn rules based on negative and positive feedback, children do show less activity in frontal and parie-

tal regions after receiving negative feedback compared to adults, consistent with the idea that the control network is still 'offline' in younger children. However, younger children showed more activity than adults in these same regions after receiving positive feedback (van den Bos, Güroğlu, van den Bulk, Rombouts, & Crone, 2009; van Duijvenvoorde, Zanolie, Rombouts, Raijmakers, & Crone, 2008). This argues against a simple model of frontal immaturity in childhood and adolescence. In addition, several studies showed that frontoparietal activity is perhaps related more to performance (Booth et al., 2004; Bunge, Dudukovic, Thomason, Vaidya, & Gabrieli, 2002; Koolschijn, Schel, de Rooij, Rombouts, & Crone, 2011) and strategy differences (Andersen, Visser, Crone, Koolschijn, & Raijmakers, 2014) rather than age per se. These findings also support the notion that the frontoparietal network can be recruited provided that performance and/or strategy use are more adult-like.

In new frameworks for adolescent brain development, several authors have argued that the field of developmental cognitive neuroscience should move towards a more comprehensive view of the developmental brain which takes into account the complex interactions between different brain regions (Casey, 2015; Johnson, 2011). One way to test this is by using connectivity analyses rather than focusing on brain activity in isolated regions. Assessing connectivity is especially important in the time period of adolescence, given the prediction derived from models of adolescent brain development that 'control regions' and 'affective regions' are unbalanced.

To date relatively few studies have tested the longitudinal development of the frontoparietal control network compared to a subcortical affective network in adolescents. In this thesis, I investigated both cognitive and affective aspects of development in a large sample of normally developing adolescents. The main questions addressed in this thesis were 1) how brain regions in the frontoparietal network develop through adolescence, and 2) how connections between affective and cognitive brain regions influence risk taking behavior.

Approach – The Braintime Study

The studies described in this thesis were all part of a larger study, the 'Braintime' project. In this project, the overarching goal was to investigate normative development of cognitive, social and affective domains in relation to brain development, hormones and genes. To this end, data was collected from 299 normally developing participants ranging from 8 to 25 years at the first time point, who were all contacted again two years later for a follow-up measurement. Of the initial 299 participants, 286 were willing to participate a second time and for 254 of them it was possible to collect a second fMRI scan (32 were excluded due to braces), resulting in a total number of 553 MRI scans collected at two time points.

Outline of current dissertation

In this thesis, I report the results from the Braintime study in which I investigated both cognitive and affective aspects of adolescent brain development. I examined this using a combination of

functional task-based MRI, resting state fMRI and structural MRI, as well as behavioral measures and hormonal assessments.

The first part of this thesis **(Chapters 2-7)** is devoted to cognitive aspects of adolescent development. I start in **Chapter 2** with an overview of the literature on the development of cognitive control and specifically cognitive flexibility in childhood and adolescence. This theoretical chapter puts forth several important questions that are addressed in this thesis. In **Chapter 3**, I present a novel experimental paradigm for a feedback learning task, which I validated in an adult sample. The task relies on multiple executive functions (inhibition, working memory and switching) and is thus a good measure to study neural reactions during cognitive control in general, and for neural reactions to positive and negative feedback in particular. The goal was to investigate whether brain regions in the frontoparietal network were mostly sensitive to the valence of feedback, or rather to the informative value of feedback. In **Chapter 4**, I describe a comprehensive study on the neural development of feedback learning in a large child and adolescent sample. In this study, my goal was to investigate normative age-related changes in neural reactions in the frontoparietal network to positive and negative feedback based on a cross-sectional sample. The question addressed in **Chapter 5** is whether age-related differences in neural activity can truly be ascribed to age or rather to differences in strategy use from childhood to early adulthood. This is an important question given that prior results on age-related changes in brain function may not actually be due to maturational processes, complicating the interpretation of earlier research. To test this question, hidden Markov models were used to detect strategies at an individual level. In **Chapter 6** I investigated longitudinal rather than cross-sectional patterns of change in the frontoparietal network. The same participants from Chapter 4 and 5 were followed-up two years later. With this paper, I assessed within-person changes and thus more accurately investigated developmental trajectories. In addition, I explored which factors contribute to developmental change over and beyond age: performance, working memory and/or cortical thickness. The final chapter in the section on cognitive development is **Chapter 7**. In this chapter, I tested whether performance and neural activity during the feedback learning task, were predictive of "real-world" learning as measured by school performance indices (reading and mathematics performance).

The next chapters **(Chapters 8-9)** concerned developmental changes in the affective domain, particularly risk taking behavior, and how this relates to brain development. Alcohol consumption was used as a real-life index of risk taking behavior in adolescence. In **Chapter 8**, I investigated the relationship between amygdala-prefrontal functional connectivity during resting state and alcohol use. It has been hypothesized that increased connectivity between subcortical and cortical regions protects against impulsive behaviors. In addition, I tested whether testosterone played a role in the relation between brain connectivity and alcohol use. Sex hormones such as testosterone rise quickly during adolescence and may explain the propensity to increased risk taking behaviors in this developmental period. Finally, in **Chapter 9**, a longitudinal follow-up

study investigating alcohol use and functional brain connectivity is described. My main goal was to investigate whether increased alcohol use follows from decreased connectivity between the amygdala and the orbitofrontal cortex (i.e., decreased connectivity influencing a person's propensity to consume alcohol), or whether instead, alcohol use precedes amygdala-orbitofrontal connectivity (i.e., a 'damaging' effect of alcohol consumption on connectivity).