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

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Chapter 10

Summary and discussion

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Adolescence is an important developmental period that is often characterized as a period of slowly emerging self-control and increased propensity to risk taking behaviors (Steinberg, 2008). It is important to investigate the mechanisms at play during adolescence in order to understand how cognitive control develops and how reckless behavior can be prevented. Several authors have constructed brain-based models to explain the phenomena of steadily increasing cognitive control from childhood to adulthood and the adolescent peak in risk taking. The most influential of these models, known as e.g. imbalance models (e.g. Ernst et al., 2006; Somerville & Casey, 2010; Steinberg, 2008) theorized that increased risk taking in adolescence can be explained in terms of relative immaturity of frontoparietal control regions in the brain, combined with a heightened sensitivity of affective brain systems in adolescence.

Although these imbalance models have sparked an increasing amount of research attention focusing on brain development in adolescence, so far relatively few large-scale and longitudinal studies have been performed. Cross-sectional studies provide a proxy of development, but no information about true developmental trajectories. Possibly as a result of this, several inconsistencies have arisen in the literature regarding development of neural activity, such as studies reporting both age-related increases as well as age-related decreases in frontal control regions (Crone & Dahl, 2012). In this thesis, I reported data from a large cross-sectional and longitudinal sample of children, adolescents and adults ranging between 8 and 27 years old. The main questions addressed in this thesis were 1) how brain regions for cognitive control develop during adolescence, and 2) how connections between affective and cognitive brain regions influence the propensity to engage in risk taking behaviors.

Development of cognitive control

In the first part of this thesis (Chapters 2-7), I examined the development of brain regions important for cognitive control using both cross-sectional and longitudinal samples. In Chapter 2, an extensive literature review of the development of cognitive flexibility was described. Cognitive flexibility is posited as one of the three main cognitive functions aside from working memory and inhibition (Diamond, 2013; Miyake et al., 2000), and refers to the ability to flexibly switch between different behaviors and the ability to adapt to a continually changing environment. Conceptually, experimental paradigms measuring cognitive flexibility can be divided into instructed flexibility and adaptive flexibility. In instructed flexibility paradigms, participants are explicitly instructed to switch behaviors (e.g., 'now only press the button when you see a green instead of a red figure'). In paradigms for adaptive flexibility, participants are not explicitly asked to switch response patterns, but instead have to infer the new correct answer based on negative feedback for a response that previously resulted in positive feedback. The studies described in this review showed that performance on both types of flexibility improved with age. However, there were differences between the two types when examining patterns of neural activity. For instructed flexibility, there appeared to be a linear increase in recruitment of brain regions for cognitive control with age. For adaptive flexibility, the pattern was more complex: regions for cognitive control became increasingly specialized in the processing of feedback with informative value. That is, brain regions for cognitive control did show activity in response to feedback in children, but these regions did not distinguish as clearly between informative and uninformative forms of feedback compared to the pattern observed in adults.

Brain mechanisms underlying feedback learning

In Chapter 3, I examined learning from positive and negative feedback in a sample of 32 adult participants (18-25 years). The goal of this study was twofold: first, to validate a paradigm to investigate neural activity in frontoparietal control regions; second, to investigate whether regions in the frontoparietal network were mostly activated after negative feedback (as reported in several earlier studies), or whether instead, these regions are better characterized as being sensitive to informative value of feedback. To test this, participants performed a feedback learning task in a 3T MRI scanner where they viewed three empty boxes with a picture presented underneath. Participants were instructed to determine which picture (out of three possible options) belonged in which of the three boxes, which could be inferred from positive and negative performance feedback. To analyze neural sensitivity to valence and/or informative value of feedback, a distinction was made between the learning phase and the application phase of the experiment. We defined the learning phase as the trials where the correct location was not yet known; therefore feedback during this phase was still informative for learning. The application phase started when participants were simply repeating correct responses they already provided before, and feedback was therefore no longer informative for learning. The neuroimaging results indicated that all regions of interest in the frontoparietal network (pre-supplementary motor area/anterior cingulate cortex (pre-SMA/ACC), dorsolateral prefrontal cortex (DLPFC) and superior parietal cortex (SPC)) were sensitive to both informative value and valence. That is, all regions were more active after informative compared to uninformative feedback, and more active after negative compared to positive feedback (possibly indicating an increased need for adaptation after receiving negative feedback). The degree to which neural regions were sensitive to informative value (i.e., the difference in activation after informative compared to uninformative feedback) correlated with behavioral performance. In addition, we used computational modeling analyses to distinguish groups based on differences in strategy use. We found that participants who employed more efficient strategies that enabled faster learning showed more activity in the frontoparietal network.

Development of the frontoparietal network in adolescence

In Chapter 4, I described a large-scale cross-sectional study in 268 participants between 8 and 25 years old, who performed the same feedback learning paradigm as described in Chapter 3. The main goal was to investigate how activity in the frontoparietal network changes across development, and importantly, whether children were also able to recruit these regions (which would argue against a strict interpretation of the frontal immaturity hypothesis in imbalance models). Several findings emerged from this study. First, I demonstrated that young children could in fact recruit regions in the frontoparietal network, albeit in different circumstances than adults. That is, activity in the frontoparietal network after receiving negative feedback increased with advancing age, as would be expected from imbalance models (which hypothesize that control regions become increasingly 'on-line' with development). However, children actually showed more activity than adults in parietal areas when they received positive feedback, supporting the notion that children can effectively recruit these areas. Second, I showed that neural reactions for negative feedback increased with age, whereas neural activity for positive feedback remained constant between ages 8 and 25. In addition, I discovered that both behavioral performance and neural activity reached adult levels around age 14-15 years, which was consistent with prior literature but was not yet confirmed in a study with a large number of participants per age group. Finally, I showed that the pubertal hormones testosterone and estradiol as well as pubertal stage did not explain additional variance above age, suggesting that areas in the cognitive control network develop relatively independent from pubertal influences.

In Chapter 5, I analyzed the behavioral data from the cross-sectional study using a different method. During the feedback learning task, participants could use reasoning strategies with different levels of complexity (e.g., a complex statistical reasoning strategy would be: 'the lion did not belong in the left box, so I am now trying this box first for the elephant', but it was also possible to complete the task by only relying on simple memory skills with no reasoning required). Markov modeling procedures were used to search whether underlying groups could be detected which differed in strategy use. The results showed that there were four different strategy groups, which differed in how advanced their reasoning strategies were. Importantly, the complexity of reasoning did not correspond directly to age, e.g., a substantial proportion of young children used more complex reasoning strategies than some of the adults. I also demonstrated that the more advanced strategy groups showed more activity in the frontoparietal network during the task. An important question I aimed to answer was whether more efficient strategy use was an explanation for the fact that older participants showed more activity in frontoparietal areas. Mediation analyses revealed that age effects on neural activity could partly be explained by strategy use, but a substantial portion of variance was still explained by age alone.

In Chapter 6, I investigated longitudinal aspects of development in frontoparietal activity. This chapter was based on data from the first time point described in Chapters 3-5, combined with data from a follow-up measurement two years later. In this study I assessed development of the frontoparietal network within individuals, rather than comparing individuals from different ages at one time point. I demonstrated that key regions in the frontoparietal network showed distinct developmental trajectories: Development of activity in the medial prefrontal cortex (pre-

SMA/ACC) was best characterized by a linear increase with age, but the SPC and DLPFC were best described by quadratic trajectories, showing a peak in adolescence or leveling off towards adulthood. An increase in behavioral performance explained additional variance above age alone for the DLPFC and SPC, whereas cortical thickness explained additional variance in pre-SMA/ACC.

Relevance for learning in real-world settings

In Chapter 7 I examined the important question whether laboratory-based learning tasks (such as the feedback learning task) which are often used to study the process of learning in tightly controlled settings, are actually predictive of learning in real-world settings such as in school. Reading and mathematics performance were used as proxies to assess real-world learning. I demonstrated that both performance and neural activity during the feedback learning task predicted reading and mathematics performance two years later. This effect remained significant even when correcting for age, working memory capacity and IQ, suggesting that feedback learning captures a unique aspect of variation in reading and mathematics performance. In addition, I showed that neural activity can predict additional variance in reading and mathematics above behavioral testing alone, highlighting the importance of neural measures in addition to behavioral measures when attempting to predict future school performance.

Risk taking in adolescence: connectivity between affective and cognitive brain regions

To get a more complete view on adolescent development I also examined affective aspects of development given that adolescent behavior is characterized by both increases in cognitive control as well as increased sensitivity to affective cues (Steinberg, 2008). To this end, I investigated whether connectivity between affective and cognitive regions is related to risk taking behavior, as would be predicted from imbalance models. In Chapter 8 and 9, I described two studies on the influence of connectivity between subcortical and cortical regions and testosterone on alcohol use in adolescents.

In Chapter 8, the goal was to investigate the relationship between alcohol use, functional brain connectivity and testosterone. To this end, resting state fMRI scans were acquired from the same participants described in Chapters 3-7. In order to collect these scans, participants were asked to lie as still as possible in the MRI scanner for five minutes with their eyes closed. Resting state functional MRI is a method for evaluating regional interactions that occur when a subject is not performing an explicit task. It is thought that individual differences in the strength of connectivity between regions in these resting state networks are related to behavior and personality traits. In this study, I specifically investigated connectivity between the amygdala and the orbitofrontal cortex. Prior studies have linked connectivity between these areas to both testosterone and alcohol use, but this was not yet investigated in a single sample nor in adolescents. In this study I showed that for boys, relatively high levels of testosterone were associated with decreased connectivity between the amygdala and the OFC. This decreased connectivity in turn was associated with increased alcohol use. In Chapter 9, I further demonstrated using longitudinal data from two time points, that amygdala-OFC connectivity at baseline predicted alcohol use two years later. Interestingly, I found no evidence for the reverse direction, i.e. alcohol use predicting later brain connectivity. This study highlighted the importance of longitudinal studies, as well as providing support for the notion that aberrant subcortical-cortical connectivity can increase the propensity for risk taking behaviors.

Discussion and future directions

Nonlinear development of the frontoparietal network

Taken together, the studies described in this thesis revealed several important findings. First, I demonstrated that recruitment of the frontoparietal network cannot be explained by a simple linear increase with age. For instance, although regions in the frontoparietal network did show an age-related increase in activity after receiving negative feedback, a number of these regions were actually more activated in children than in adults after receiving positive feedback (Chapter 4). Furthermore, the results from a longitudinal study presented in this thesis (Chapter 6) revealed that frontoparietal activity increases in a nonlinear way with age in the DLPFC and SPC. Most prior studies used cross-sectional comparisons, relatively small sample sizes and/or discrete age groups (e.g. 8-12, 13-17 years) rather than assessing the whole age range from late childhood to early adulthood, which possibly explains contradictory findings in the literature regarding neurocognitive development. The work described in this thesis demonstrates the benefits and importance of using large sample sizes and longitudinal designs to effectively determine neurodevelopmental trajectories.

The findings of nonlinear development with age are not entirely consistent with simple models of frontal immaturity as predicted by imbalance models. The results from Chapter 4 and 6 showed that frontoparietal regions are not simply 'offline' or underdeveloped in childhood, but instead that they are involved during different processes compared to adults. In Chapter 6, I found support for a quadratic pattern with an adolescent peak or leveling off in late adolescence in behavioral performance and recruitment of SPC and DLPFC. A similar peak in behavioral performance for 17-year olds during executive functions tasks was reported previously (Taylor, Barker, Heavey, & McHale, 2013). These results fit better with the model of adolescent brain development posited by Crone and Dahl (2012), who hypothesized that adolescence can be characterized as a period of increased flexibility for recruitment of cognitive control regions. That is, the framework predicts that the range of possible behavioral and neural outcomes may be larger in adolescents than in adults depending on motivation or salience. For instance, in a 'hot context' when motivation is high (e.g. when peers are present or when monetary incentives are offered), performance and neural activity may be relatively more enhanced in adolescents than in adults.

Although most prior research has focused on peer presence effects on risk taking behavior (e.g. Chein, Albert, O'Brien, Uckert, & Steinberg, 2011), it has been shown that the presence of peers also influences performance on cognitive tasks such as relational reasoning (Wolf, Bazargani, Kilford, Dumontheil, & Blakemore, 2015). Also, recent research showed that adolescents recruit the frontoparietal network to a greater extent than adults for decisions associated with a greater monetary reward (Teslovich et al., 2014) and during relatively complex paradigms such as creative divergent thinking (Kleibeuker et al., 2013). However, relatively few studies have explored increased flexibility of adolescent cognition, thus further research is necessary to confirm this intriguing hypothesis.

Unraveling the mechanisms underlying cognitive development is especially important given the potential relevance for learning in school settings. In Chapter 7, I demonstrated that both behavioral performance and neural activity during a feedback learning task were predictive of reading and mathematics performance two years later. An interesting discussion that is relevant for school interventions is whether children learn better from positive compared to negative feedback. In Chapter 4, I found no evidence at the behavioral level that children learn relatively more from positive than from negative feedback: Children learned less overall from feedback compared to adults, but there was no developmental difference in the ratio of learning from positive compared to negative feedback (but see van Duijvenvoorde et al., 2008). However, the finding that frontoparietal activity for negative feedback increased with age, whereas activity for positive feedback remained constant with age, may indicate that processing negative feedback requires more effort as indicated by increased recruitment of cognitive control regions by adults. Negative feedback may be inherently more difficult than positive feedback, because an additional inference has to be made which demands more from the cognitive system (e.g. if response A received negative feedback, the child must infer that a switch to another answer is necessary). This particular feedback learning paradigm was relatively easy, but when the frontoparietal system is increasingly taxed, such as when multiple tasks are performed at the same time, a developmental difference in the relative learning rate from positive and negative feedback may become apparent. Encouraging teachers to focus more on positive rather than negative feedback may improve children's performance because positive feedback demands less from the developing cognitive system, but this needs to be confirmed in further research.

With regard to the adolescent period, I argue that it is important to focus not only on adolescent deficiencies in executive functioning, but also on the unique possibilities of the adolescent brain given the right incentives. New models of adolescent brain development (Casey, 2015; Crone & Dahl, 2012; Johnson, 2011) and preliminary evidence (Teslovich et al., 2014; Wolf et al., 2015) suggest that adolescents may benefit relatively more than other age groups from for instance social feedback from peers and affective rewards in relation to cognitive performance. Pursuing this research further may have important implications for educational practice and may lead to programs that are better suited to the specific challenges of the adolescent brain.

Individual differences influencing frontoparietal recruitment

Aside from age-related changes in recruitment of the frontoparietal network, I found evidence for other factors influencing the level of frontoparietal recruitment during a feedback learning task. This is an important line of research given that age-related changes interpreted in prior studies, may in fact be explained by individual differences in behavioral or neural measures rather than by development. In this thesis, I demonstrated that increased behavioral performance (defined as the percentage of feedback correctly used in further trials) corresponded to increased frontoparietal activation, even when correcting for age. The findings from Chapter 5 furthermore indicated that a portion of age-related increases in neural activity during a feedback learning task was mediated by differences in strategy use. That is, not only increased age, but also more efficient strategy use was related to increased recruitment of the frontoparietal network. Therefore, it was possible that young children who used relatively advanced reasoning strategies, showed more frontoparietal activity than adults who used less advanced strategies. Other individual differences I investigated in relation to cognitive development were cortical thickness (Chapter 4 and 6), working memory (Chapter 6), sex hormones and pubertal development (Chapter 4). I demonstrated that cortical thickness explained variance above age in pre-SMA/ACC activity, but working memory and sex hormones did not explain additional variance in frontoparietal recruitment.

It is important that new models of adolescent brain development theorize on the contribution of individual differences to developmental changes in neural activity. The individual differences I tested in thesis, i.e. task performance, working memory, cortical thickness and pubertal development, are so intricately linked with development that it is currently not certain whether they should be studied separately from age. It is an interesting theoretical discussion whether these individual differences should be regarded as a crucial part of development, or whether these are factors that should be corrected for so that pure age-related differences remain. Related to this issue, in Chapter 4 I found no relation between sex hormones and cognitive performance or frontoparietal activity. This is consistent with prevailing developmental theories which hypothesized that cognitive brain systems develop relatively independently from hormonal influences (Nelson et al., 2005; Steinberg, 2008). This may indicate that advancing age and pubertal development are separable processes that should be studied independently.

With regard to the relevance of studying individual differences for learning in school settings, it is intriguing that I found a relation between feedback learning performance and neural activity for feedback that is informative compared to feedback that is not informative for learning. Therefore it is possible that, the larger the difference between neural activity for learning vs. applying rules, the more sensitive these neural areas are to learning signals. This neural difference may be an interesting brain-based index of learning capacity that should be explored in further research, especially given the relation I found between this measure and future reading and mathematics performance (Chapter 7). In addition, my research provides preliminary reasons for educators to focus more on teaching children different cognitive strategies, as the results in this thesis demonstrated that more advanced reasoning strategies were associated with increased frontoparietal recruitment. Prior research also suggested that development of feedback learning performance is better characterized by abrupt increases in performance due to a strategy switch, rather than slow, incremental changes (Schmittmann et al., 2012).

Adolescent risk taking and subcortical-cortical functional connectivity

In another line of research described in this thesis (Chapters 8 and 9), I investigated connectivity between cortical and subcortical regions and their relevance for risk taking behavior. I discovered that there is a relation between reduced amygdala-orbitofrontal cortex connectivity during resting state and increased alcohol intake. Longitudinal analyses showed that brain connectivity preceded alcohol use two years later, suggesting that aberrant brain connectivity influences an individual's future propensity to engage in risk taking behavior.

Although connectivity research is a relatively new topic of scientific interest, it is especially important to investigate connectivity during adolescence, given that imbalance models posit that risk taking can be explained in terms of an imbalance between emotional and cognitive brain systems, i.e. an inability of the cognitive system to 'put the brakes on' the affective system. This fits with the findings I reported in Chapter 8 and 9, which showed that decreased connectivity between the amygdala (seen as part of the affective brain system) and the medial frontal cortex was associated with increased alcohol consumption. Possibly, decreased connectivity corresponds to decreased (frontal) control over (subcortical) approach tendencies. On the other hand, increased connectivity between these regions may protect against risky decisions such as the choice to consume alcohol, for instance by increased top-down frontal control over more 'emotional' brain systems. Other research in line with imbalance accounts showed that with development, there is a decrease in the strength of local short-range connections (e.g. cortical-cortical, subcortical-subcortical connections) and an increase in more distal long-range connections (e.g. subcortical-cortical) in number and strength (Fair et al., 2009). However, with regard to the specific coupling between the amygdala and the OFC, it should be noted that I did not find evidence for age-related changes in connectivity using a large-scale longitudinal assessment over two time points.

Another interesting discussion surrounding imbalance models is whether risk taking should be seen as purely a societal problem, or also as a normal and perhaps even adaptive aspect of development. For alcohol specifically, it could be argued that alcohol use is in fact normative during adolescence, given the high prevalence during this developmental period (Hibell et al., 2012). It has also been shown that alcohol use is associated with popularity (Balsa, Homer, French, & Norton, 2011), indicating a socially rewarding and adaptive effect for alcohol use. For risk taking in general, several authors have argued that it is both a normal and adaptive characteristic of adolescence (Casey, 2015; Crone & Dahl, 2012). That is, it has been posited that a certain level of explorative behavior and increased independence from parents is both a necessary and beneficial aspect of adolescence. Consistent with the idea that exploration/risk taking during adolescence is adaptive, is the fact that other animals also experience a juvenile period characterized by increased exploration, more fighting with parents and increased interest in same-aged peers (Casey, 2015).

Limitations and future directions for longitudinal research

Although the studies described in this thesis make an important contribution to the literature on adolescent brain development, several limitations need to be taken into account when interpreting these findings. Below I make several recommendations for future research which I believe will be crucial in order to advance our understanding of the developing brain.

The studies described in the first part of this thesis fit with recent models of adolescent brain development which emphasize increased flexibility of the frontoparietal control system during adolescence (Crone & Dahl, 2012; Johnson, 2011). Thus, adolescents may be more sensitive to manipulations of motivational context compared to children or adults. However, it should be noted that for the studies described in this paper, it was not possible to assess motivational salience nor was this explicitly manipulated with e.g. peer presence or monetary incentives. An interesting direction for future research would be to investigate influences of motivational salience on cognitive performance and frontoparietal recruitment in adolescents. Moreover, this hypothesis can also be tested by developing motivation-based interventions in schools that are tailored to the specific sensitivities of the adolescent brain.

In future studies, it will also be important to not only examine neural activity per se, but also connectivity between regions and its relation to cognitive development. For instance, Casey (2015) recently argued in favor of a circuit-based account of adolescent development, which takes into account connectivity between e.g. subcortical and cortical regions and more extensive brain networks. In Chapters 8 and 9 I investigated how neural connectivity between two brain regions is related to risk taking behavior. However, the relation to cognitive performance was not yet investigated in this thesis. It should also be noted that with the resting state methods employed in these chapters, it was not possible to determine whether activity in the OFC down-regulated amygdala activity or whether amygdala activity modulated OFC activity. Techniques such as dynamic causal modeling may unravel the direction of subcortical-cortical connectivity in relation to adolescent risk taking.

Another important step forward would be to assess participants at more than two time points, in order to pinpoint developmental trajectories in even more detail. This will allow for higher-order polynomial age functions to be tested within individuals, which is not possible with two time points. In addition, a broader selection of paradigms to measure cognitive functioning and risk taking behavior is needed in order to validate that the results presented in this thesis not only hold for this specific performance monitoring paradigm or to this particular questionnaire for alcohol consumption. With regard to hormonal measurements, it should be tested whether the finding that cognitive development occurs independently from hormonal influences can be replicated. Other factors may also explain the lack of an effect, such as the timing of data collection for post-menarcheal girls (on the 7th day of the menstrual cycle rather than the day of the scan).

Taken together, future research should further test new models of adolescent brain development taking into account the complex environmental influences on adolescent behavior (Casey, 2015; Crone & Dahl, 2012) using similar large-scale longitudinal samples but a broader variety of measurements and more advanced techniques.

Conclusion

In conclusion, this thesis provides a comprehensive overview of both cognitive and affective aspects of development in relation to neural maturation and pubertal hormones. The results speak to a debate about imbalance models of adolescence, and provide evidence that a more nuanced description of development in frontoparietal control regions is needed. The results have important implications for constructing new theoretical frameworks and may eventually contribute to the advancement of educational interventions that are better tailored to the challenges and possibilities of the teenage brain.