Adolescent risk taking : the influence of pubertal development, neural responses to rewards and social context

Braams, B.R.

Chapter 7

Summary and General Discussion

Adolescence is a developmental period associated with increases in risk taking behavior. There is preliminary evidence that risk taking behavior is related to pubertal development (Collado, 2014), reward related neural responses (Galvan, 2007), and social context (Chein et al, 2011). The goal of this thesis was to further investigate relevant factors for risk taking behavior in adolescence and to investigate the relationship between these factors. The chapters in this thesis are centered around three main questions. The first question is whether striatum responses are hypo- or hyperactive in adolescence, and how pubertal development and testosterone levels are related to this response. The second question concerns the influence of social context. We tested which aspects of social context interact with reward processing regions and how social brain regions develop with age. The last question is how age, puberty and neural responses to rewards influence real life risk taking behavior. In the discussion, first the main findings of each chapter are briefly summarized, after which the implications for the imbalance model are discussed. The discussion ends with directions for future research and general conclusions.

Summary

The first empirical chapter, **Chapter 2**, describes the effects of social context on reward processing and the validation of a new paradigm. Adolescence is a time in which peers become very important (Dahl, 2004). Adolescents spend more time with their peers than children and adults, and risk taking behavior often occurs in groups (Steinberg, 2004). It has been shown that being observed by a peer increases risk taking behavior on a task and striatum responses during the task (Chein et al, 2011). However, it is not known which aspects of the social context are driving this effect. In this chapter this question was investigated, with a specific focus on whether thinking about a peer affects striatum responses.

We developed a new paradigm; participants played a game in which they could win and lose money for themselves, their best friend and a disliked other. We hypothesized that a set of cortical and mid-line structures that have previously been identified in studies investigating the social brain, i.e. temporo-parietal junction (TPJ), precuneus and medial pre-frontal cortex (mPFC), would respond to social context and that the ventral striatum, a key region for reward processing (Delgado, 2007), would respond to reward information. In a sample of young adults we confirmed these hypotheses. Results showed that TPJ, precuneus and mPFC respond to social context, and that ventral striatum distinguished between winning and losing. The only region in which an interaction between social context and reward information was found was the ventral striatum. When playing for self and for a best friend the striatum was more active when winning than when losing. However, this pattern was reversed when

receiving outcomes for a disliked other. In this case the striatum was more active when losing than winning. This indicates that ventral striatum responses are dependent on the beneficiary. These results were mirrored in subjective ratings. Participants rated how they felt when winning and losing for each of the beneficiaries. The fact that striatum responses and subjective ratings showed a similar pattern strengthens the interpretation that the striatum signals subjective pleasure. To further test how these patterns of responses in social brain areas and the striatum change with age, we investigated the developmental pattern of these responses in the next chapter.

Chapter 3 describes the results of study in which a large sample of 299 participants between 8 and 25 years of age played the gambling game described in **Chapter 2**. The imbalance model (Somerville et al, 2011) proposes hyperactivity of the ventral striatum in adolescence. Previous studies testing this model found mixed results regarding the specificity of striatum activation during adolescence, with some studies finding hyperactivation of the striatum (Christakou et al., 2011; Ernst et al., 2005; Galvan et al., 2006; Van Leijenhorst et al., 2010a, Van Leijenhorst et al., 2010b) and others hypo-activation of the striatum (Bjork et al., 2004; Bjork et al., 2010). Possible explanations for this inconsistency in results are the use of relatively small samples and inclusion of different age groups to compare striatum responses in childhood, adolescence and adulthood (for a review see Richards et al., 2013).

In this study, we used a large sample with continuous age range. The findings from the adult sample were replicated in this sample: ventral striatum responses were linked to winning versus losing, whereas social brain regions such as the TPJ, precuneus and mPFC were selectively active for social context information. To follow up on the whole brain results and to identify regions in the brain that showed hyperactivity in adolescence, a whole brain regression with age was performed. In this analysis the ventral striatum was identified as a region that shows hyperactivity in adolescence. Furthermore, the results showed that this peak was specific for playing for self. The whole brain quadratic regressions for friend and antagonist did not yield significant results in the striatum. This means that striatum responses in adolescence are not always hyperactive, but that this is dependent on the social context in which rewards are received. A study by Chein et al. (2011) showed that striatum responses are elevated when peers are present and that these responses are even more elevated in adolescence. Combining the current study with this study, it appears that receiving rewards *for* others is different from receiving rewards for self when others are *present*. Possibly receiving rewards for others is related to social skills such as perspective taking or friendship quality. Indeed, we found a relationship between striatum responses to winning versus losing for a friend and reported friendship quality.

Chapter 4 zoomed in on striatum responses when playing for self and used longitudinal data. One of the main advantages of a longitudinal design, compared to a cross-sectional design is the possibility to test both between- and within-subject effects. Furthermore, a longitudinal design is sensitive to subtle individual differences. A large sample with continuous age range not only provides the opportunity to test for continuous developmental effects, but also to test whether individual difference variables such as pubertal development or risk taking tendency explain additional variance in striatum activation above age.

First it was tested whether the peak in striatum responses during adolescence could be confirmed in the longitudinal data set. The peak in striatum activation during adolescence was confirmed. Results showed that this peak was specific to the nucleus accumbens, a part of the ventral striatum. Besides the effects of age, the influence of puberty was also tested. Although all adolescents go through puberty, not all do so at the same pace. This means that adolescents of the same age could be in a different stage of pubertal development. Previous studies have shown a relationship between testosterone, a hormone associated with puberty, and neural responses to rewards (Op de Macks et al, 2011). To test the influence of pubertal development and pubertal hormones, we investigated whether pubertal development, measured with the Pubertal Development Scale (Petersen et al., 1988) and salivary testosterone levels, were related to nucleus accumbens responses to rewards. Results showed that testosterone was positively related to nucleus accumbens activation. However, these models were not corrected for age. When corrected for age, there was no relationship between testosterone and striatum responses to rewards, probably because chronological age is highly associated with testosterone levels. We also tested whether personality was related to neural responses to rewards. Results showed that the willingness to put effort into obtaining a reward, as measured with the Drive scale of the Behavior Inhibition System/Behavior Activation System (BIS/BAS) questionnaire (Carver & White, 1994), was positively related to the ventral striatum response to rewards. This relationship was not found cross-sectionally. This highlights the importance of a longitudinal design and indicates that the changes in striatum responses to rewards and changes in motivational drive are associated with each other, but that the absolute values do not correlate.

Chapter 5 describes longitudinal changes in social brain areas. Social development is one of the key goals of adolescence. During adolescence, perspective-taking skills increase and friendships become more intimate and complex (Rubin, Fredstrom, & Bowker, 2008). The restructuring of adolescents' social environment and the changes in social skills, go hand in hand with changes in the brain. Since the focus of this study was on the effects of social context, irrespective of outcome of the gamble, responses

to winning and losing were averaged in the analyses for this chapter. In this chapter we focused on playing for self and friend. Results showed that playing for a friend, compared to playing for self, resulted in activation in the TPJ, precuneus and mPFC. All of which are regions related to social information processing (Blakemore, 2008; Van Overwalle, 2009). Developmental patterns in all regions showed that as participants get older, the neural responses to playing for a friend become more similar to the neural responses when playing for self. To follow up on these results, we tested whether the developmental patterns for playing for a friend and for self showed a different trajectory. In other words, we tested whether activity in social brain areas showed a linear increase (or decrease) over age, or a peak in adolescence. Results showed different developmental trajectories for playing for friend and playing for self in the same neural region. More specifically, in the dmPFC activation related to playing for self showed a peak in adolescence whereas in this region the activation related to playing for a friend remained the same over development. In the TPJ both activation for thinking about a friend and self is decreased over age, but friend related activity decreased more rapid.

Perspective taking is the ability understand the emotions and intentions of others, for instance when someone else is upset that you understand why. In **Chapter 5** it was tested whether differences in recruitment of the social brain areas was related to individual differences in how well participants reported to be able to take someone else's perspective. Previous studies reported a relationship between perspective taking and activity in social brain areas (Ruby & Decety, 2004). However, in this study we did not find a relationship between perspective taking skills and activity in social brain areas. This study differs from other studies investigating social responses. In most studies, participants are required to think about personality traits of different persons, or mentalize about others' intensions (for a review, see Blakemore, 2008). Those type of studies require much higher social processing compared to winning or losing for someone else, without the explicit instruction to think about what winning or losing would mean for that person or how they would feel. This study shows that low level social processing is related to activation in social brain areas and that this network is established at a young age. Children as young as 8 are already capable of recruiting these brain areas and possibly, differences occur when social information processing is challenged. Challenges in this case could be perspective taking or mentalizing about others' feelings and intentions. This might explain why we did not find a relationship between perspective taking and neural activation in the TPJ and mPFC. In other words, if every participant performs at ceiling level, there are no individual differences to relate to other measures.

Adolescence is associated with increased risk taking behavior in real life. **Chapter 6** describes the relationship between neural responses to rewards and real-life risk taking behavior. Most risk taking behavior is normative, but excessive risk taking can have adverse effects. Risk taking behavior can be expressed in substance use, alcohol use or traffic related risks. Identifying relevant factors for risk taking behavior is an important step towards preventing excessive risk taking behavior. Proposed relevant factors are ventral striatum hyperactivity during adolescence (Galvan, 2007) and pubertal development (Collado, 2011). The measure for real-life risk taking behavior in this study was alcohol consumption. Alcohol consumption can be considered risky behavior due to the known adverse effects on health. It is especially risky for young adolescents, not only for the presumed negative influence of alcohol on the developing brain, but also since alcohol consumption is illegal for those adolescents who have not yet reached the legal drinking age.

In this chapter it was assessed whether self-reported alcohol use was related to neural responses to rewards during the fMRI gambling task and pubertal development. Expected was that those adolescents who showed higher neural responses to rewards during the fMRI task would also report higher alcohol use. In this study we again used longitudinal data, which allowed us to test cross-sectional relationships as well as predictive relationships between testosterone, neural responses to rewards and alcohol use. As hypothesized, we found that higher nucleus accumbens responses during the task were related to more alcohol use. Furthermore, testosterone levels were predictive of alcohol use. In other words, those participants who had relatively high levels of testosterone at the first time point, reported higher alcohol use at the second time point.

Implications for the imbalance model

The imbalance model proposed by Somerville et al, (2011) describes an imbalance development of subcortical and cortical brain regions. Subcortical regions, regions involved in affective processing such as the ventral striatum, are thought to develop faster than the prefrontal regions, which are involved in executive functions. The interplay between the overactive subcortical regions and the not fully developed prefrontal cortex results in a drive towards rewards and risk taking. This model provides a framework to understand some of the changes observed in adolescence. One aspect that the model is not specific about is which factors might be driving the hyperactivation of the subcortical regions. The studies in this thesis were set out to test development of the ventral striatum and to refine the imbalance model by investigating which individual difference factors influence ventral striatum activation. The factors of interest were chronological age, pubertal development, personality and social context.

The first question concerned whether ventral striatum responses showed hypo- or hyperactivity during reward processing. The results described in this thesis show that neural responses to rewards are elevated during adolescence and that this response is specific to the nucleus accumbens, a primary reward area and part of the ventral striatum. The elevated nucleus accumbens response during adolescence is consistent with predictions from the imbalance model (Somerville et al, 2011). The next question was how individual differences in pubertal development and personality relate to individual differences in nucleus accumbens responses. Although the general trend is toward elevated responses during adolescence, nucleus accumbens responses show large individual differences. These differences are evident in both the absolute values of response at a certain time point as well as in the effects over time. In other words, cross-sectionally some children and adults show higher responses than adolescents, and longitudinally some children show an expected increase in their response over time whereas other show a decrease and vise versa in adulthood. Explaining this variation in nucleus accumbens responses was one of the focus points of this thesis. We investigated whether pubertal development (PDS and testosterone levels) and personality (BAS Drive) were related to nucleus accumbens responses. Results showed that participants with higher levels of testosterone, also exhibited higher nucleus accumbens responses to rewards. This same relationship was found between BAS Drive and the nucleus accumbens response. Lastly, we were interested in how the nucleus accumbens response changes as a function of context information. In previous studies it is shown that the nucleus accumbens flexibly responds to different reward magnitudes (Galvan, Hare, Parra, Penn, Voss, Glover, & Casey, 2006) and contexts (Fareri, Niznikiewicz, Lee, & Delgado, 2012). In the studies in this thesis different social contexts were used. Results showed that winning money for self results in different activation than winning money for a friend or disliked other. This means that contextual information is an important factor in nucleus accumbens responses to rewards. Taken together, the results in this thesis show that nucleus accumbens responses to rewards peak in adolescence, that there are large individual differences in the nucleus accumbens response, and that age, pubertal development, personality and social context influence nucleus accumbens response to rewards. These results can be used to refine the imbalance model.

The imbalance model proposes hyperactivity of the nucleus accumbens in adolescence, but does not specify the conditions under which nucleus accumbens responses to rewards are hyperactive in adolescence. The studies in this thesis show that the nucleus accumbens is specifically active when winning money for self and a friend, rather than for a disliked other. However, only when winning for self does the nucleus accumbens peak in adolescence. This shows that the nucleus accumbens activation is related to motivation and that the imbalance model is only valid when

rewards are self-relevant. Furthermore, the imbalance model does not take personality differences into account. The studies in this thesis show that there are large individual differences in nucleus accumbens response and that these differences are related to personality factors. Besides the quadratic trajectory of development for the nucleus accumbens, resulting in a peak of activation in adolescence, the imbalance model proposes linear development of the prefrontal cortex. Although linear development of the pre-frontal cortex has been shown in a study investigating structural changes over development (Mills, Goddings, Clasen, Giedd, & Blakemore, 2014), this thesis shows that functional activation over development of the prefrontal areas can also show a non-linear, i.e. quadratic, developmental trajectory. In the medial pre-frontal cortex a quadratic pattern over development was observed for receiving outcomes for self, and when winning versus losing for an antagonist. Future studies are needed to investigate whether other areas of the pre-frontal cortex show non-linear development and under which conditions.

Limitations and future directions

All studies in this thesis are based on a reward task in which participants could win and lose money. This task has been successful in showing responses in expected brain areas and these neural responses were related to individual differences. Furthermore, neural responses and individual difference variables were related to real life risk taking behavior. Importantly, in the current task no aspect of risk taking was included. The gamble at the beginning of the trial did not influence outcome probabilities and there was no option not to play, i.e. to pass. To get a handle on complex behavior, such as real life risk taking behavior, there are many merits of starting off with a simplified version of a task in which some ecological validity is traded off for high experimental control. Undeniably, real life situations are vastly different from such a paradigm. The factors identified in this research should be tested and validated in other, more ecologically valid, paradigms. These paradigms should include an aspect of risk, in which probabilities and levels of outcome are manipulated to capture risk taking behavior. Furthermore, behavior/outcome contingencies in real life are often ambiguous. The chances of getting into a car accident or getting caught by the police are not explicit. There is preliminary evidence that especially adolescents are differentially sensitive to varying levels of ambiguity (Tymula, Rosenberg Belmaker, Roy, Ruderman, Manson, Glimcher, & Levy, 2012): a notion that should be tested further in the future.

On the far end of the spectrum between experimental control and ecological validity is real life risk taking behavior. A good way to capture real life behavior is to use an experience sampling method. In a study that uses this method, participants are prompted at random intervals throughout the day to answer a few short questions about

what they are doing and with whom. This provides an ecologically valid measure of participants' behavior. Future studies could link these observations to other variables, such as age, puberty, personality and social context.

In this thesis different factors that influence real life risk taking behavior were identified. At the neural level the main factor of interest was on the nucleus accumbens. The nucleus accumbens is an important brain region for reward processing. However, from connectivity and network analyses it is known that neural regions do no operate alone, but that the brain is a highly complex system in which different areas communicate with and influence each other. One approach to measuring network connectivity is using a resting state functional connectivity approach. In such an approach participants are asked to lie still in the scanner for approximately ten minutes and they are instructed to just let their mind wander. Spontaneous connectivity between different brain areas is captured with a resting state approach. Studies have shown that resting state connectivity between affective regions and prefrontal regions is related to alcohol use in adolescents (Peters, Jolles, Van Duijvenvoorde, Crone, & Peper, 2015). New, cutting edge techniques, are being developed that will allow us not only to identify networks, but also to investigate the temporal dynamics of these networks. The first studies using this technique show that the brain cycles through different network states. In a certain network state some areas are highly connected with each other, which areas are highly connected varies per state (Hutchison & Morton, 2015). This new dynamic network analysis provides a promising new direction to understand how the brain is connected and how network connectivity is related to behavior.

In the studies in this thesis, the influence of puberty was assessed with measures of pubertal status and testosterone levels. We showed an effect of baseline levels of testosterone on nucleus accumbens activation. However, the exact mechanism by which testosterone influences nucleus accumbens activity remains speculative. Effects of testosterone can both be slow and acute (Goetz et al., 2014). A slow effect is the organizing role in brain development of testosterone through a complex cascade of genomic effects, whereas an acute effect could be for instance the rise in testosterone in response to a threat or a sexual stimulus. In the studies described in this thesis, participants collected saliva at the beginning of the day, directly after waking up. This measurement captures baseline levels of testosterone. It is likely that baseline levels are related to slow effects of testosterone, such as structural brain reorganization. These changes in structure could then be reflected in brain function. This would explain why we found a relationship between nucleus accumbens activation at the second time point and alcohol use at the second time point. Acute effects of testosterone are presumably related to brain function. In testosterone administration studies, changes

in risk taking behavior (Van Honk et al., 2004) and nucleus accumbens activation were found (Hermans et al., 2010). Acute effects could be captured by measuring naturally fluctuating testosterone levels, which could be done by sampling testosterone levels in close proximity to the fMRI task. In such a way testosterone reactivity to the task would be measured. Higher testosterone reactivity during the task could be related to alcohol use. Future studies could focus on this hypothesis.

Personality was the last factor that was focused on. A relationship was found between the drive to obtain rewards and nucleus accumbens activation during the gambling task. However, personality is a very broad construct and does not only comprise a drive for rewards. Another factor that has been shown to influence risk taking is impulsivity (Peper, Mandl, Braams, de Water, Heijboer, Koolschijn, & Crone, 2013). Those individuals who are more impulsive also take more risks on a risk taking task. Impulsivity is a multidimensional construct and comprises at least three factors: acting without thinking, impatience and sensation/novelty seeking (Robbins, Gillan, Smith, de Wit, & Ersche, 2012; van den Bos, Rodriguez, Schweitzer, & McClure, 2015). A recent study showed that of these three factors impatience was most related to adolescent specific impulsive behavior. Possibly impulsivity, or more specifically impatience, and a high drive for rewards interact. That is to say, if an individual has a high drive for reward and is highly impulsive (impatient), this combination may lead to risk taking behavior Future studies should investigate whether these two factors interact and how.

Peer influence was not a factor that was investigated in this thesis. However, adolescent risk taking behavior often occurs in groups and peers are an important influence on adolescent behavior. One of the first studies to test whether peer presence influenced risky decision making used a driving game in which participants encountered several stoplight and could decide whether they would run the yellow light and take a risk, or to stop (Chein et al., 2011; Gardner & Steinberg, 2005). Adolescent participants showed increased risky decisions when peers were present. This effect has now been replicated in several other studies (O'Brien, Albert, Chein, & Steinberg, 2011; Smith, Halari, Giampetro, Brammer, & Rubia, 2011; Weigard, Chein, Albert, Smith, & Steinberg, 2014). Exciting new research has shown that peers do not only have a negative influence on adolescent behavior, but that peers who favor a pro-social attitude can trigger pro-social behavior in adolescents (Van Hoorn, Van Dijk, Meuwese, Rieffe & Crone, 2014). This shows that peer influence is situational and that adolescents can flexibly adapt to the peer norms. A crucial question concerns the mechanism behind this effect. In other words, which properties of a peer influence behavior? Future studies could focus on whether personality, i.e. risk taking or risk averse, and other variables such as age and sex are important for this effect.

Conclusions

Taken together, the studies in this thesis show that neural responses to rewards in the striatum are elevated during adolescence. This response is influenced by chronological age, pubertal development, personality and the social context. Importantly, the striatum response to rewards is related to real life risk taking behavior and therefore has functional relevance. The results of this thesis provide vital insight in the complex relationship between reward processing and real life risk taking behavior. Some amount of risk taking in adolescence is normative and should not be problematized. However, some health compromising behaviors that find their onset in adolescence may become lifelong habits. Understanding which factors may lead to excessive risk taking in adolescence could help prevent adverse effects of this behavior in adulthood.