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

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# Chapter 1

## General Introduction

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Adolescence, defined as the transition phase between childhood and adulthood, is a time of many physical, cognitive and social-emotional changes. It is a natural time of exploring, thrill seeking, and for eventually setting long-term goals and aspirations (Crone & Dahl, 2012; Dahl, 2004; Steinberg, Albert, Cauffman, Banich, Graham, & Woolard, 2008). The first phase of adolescence (also defined as early- to mid-adolescence) starts with the onset of pubertal maturation around age of 10-11 years (but approximately 1.5 years earlier for girls than for boys) and lasts until approximately ages 15-16 (Shirtcliff, Dahl, & Pollak, 2009). At the onset of puberty, a dramatic increase in the secretion of adrenal androgens, gonadal steroids, and growth hormone causes many changes in physical appearance (e.g., facial and physical changes) and changes in brain regions with high receptor density for gonadal hormones such as testosterone and estradiol (Scherf, Berman, & Dahl, 2012). Following pubertal maturation, the second phase of adolescence (also defined as mid-to-late adolescence) starts approximately at age 15-16 and lasts to age 21-22, during this phase adolescents gradually reach independence from parents and obtain mature social goals (Steinberg, et al., 2008; Steinberg & Morris, 2001). One of the most prominent findings in observational studies, (i.e. correlational studies) is that adolescents take more risks than children or adults (Beyth-Marom & Fischhoff, 1997; Boyer, 2006). The focus of this thesis is on adolescent risk taking behavior. The goal is to identify individual difference factors that are related to risk taking behavior and assess how these variables change over development.

**Risk taking in adolescence**

Risk taking is defined as engagement in behaviors that are associated with potentially negative outcomes. Adolescents take more risks than children and adults (Beyth-Marom & Fischhoff, 1997; Boyer, 2006). For example, adolescents are more likely to have casual sexual partners, engage in binge drinking, get into car accidents and seem to act without thinking about the long term consequences of their actions (Eaton, Kann, Kinchen, Shanklin, Ross, Hawkins, Harris, Lowry, McManus, Chyen, Lim, Brener, & Wechsler, 2008; Steinberg, et al., 2008). In a striking juxtaposition, although adolescents are physically in the best condition of their lives, mortality rates go up by 200-300% compared to children (Dahl, 2004). This mortality is primarily due to preventable causes such as getting involved in accidents, driving under the influence and engaging in high-risk behaviors under pressure from peers/with friends. One example is driving with friends, which encourages reckless driving (presumably to show off and impress peers but the mechanisms are not fully understood; see Steinberg, 2008).

Adolescents can assess risks and can reason logically when they are asked about risks or consequences (Boyer, 2006). For example, in a study using a risk taking task in which the demands on learning and working memory are minimized by making outcome values and associated probabilities explicit (Van Leijenhorst, Westenberg, & Crone, 2008), decision-making behavior did not differ from age 8 to 30 on this task. This suggests that from late childhood on participants are able to take both reward and probability information into account when making decisions. The increase in risky decision making observed during adolescence is therefore most likely not only related to cognitive immaturities, but rather to a combination of cognitive, emotional and social factors that lead to increased risk taking behavior (Crone & Dahl, 2012; Steinberg, et al., 2008). In line with this, a recent meta-analysis revealed that adolescents take more risks than children and adults, but only in situations where there is no sure/safe option (Defoe, Dubas, Figner, & van Aken, 2014). Understanding which factors contribute to risk taking behavior is of great importance to eventually change behavior and for preventing adverse consequences of risk taking in the future. Behavioral studies have yielded important results, but do not inform us about the neural mechanisms behind risk taking behavior. Understanding the neural mechanism could provide important information on which adolescents are more predisposed to take risks.

**A neuroscientific model to understand risk taking in adolescence**

From a neuroscientific perspective, several partly overlapping and partly complementary theoretical models have been proposed about how trajectories of brain maturation may explain behavioral changes in adolescence. Even though the models have broader goals than solely understanding risk taking in adolescence, they provide intriguing hypotheses with respect to the question of why adolescence may be a vulnerable period for risk taking.

The model that is probably most explicit in hypothesizing about risk taking in adolescence is the imbalance model postulated by Somerville, Jones and Casey (2010). According to this model, there is an imbalance between the development of subcortical brain regions, such as the ventral striatum, and the pre-frontal cortex. The development of the ventral striatum precedes development of the pre-frontal cortex. The ventral striatum is involved in reward processing and decision-making based on incentives (Delgado, 2007). The pre-frontal cortex is involved with tasks such as planning, inhibition and cognitive control more generally (Miller & Cohen, 2001). The interplay between a not fully developed pre-frontal cortex, which is therefore not fully capable of executing control related functions, and further developed emotional areas such as the ventral striatum causes an imbalance resulting in a primarily emotion driven approach to rewards and risks in mid-adolescence.

To test this model, empirical studies available to date have mostly used functional Magnetic Resonance Imaging (fMRI). fMRI is a safe and non-invasive technique, which allows for the study of neural activation during specific phases of a task. These studies have focused on two task-related processes that are important for risk taking investigation: reward anticipation and responses to receiving a reward (although others have also distinguished between other phases, such as cue-related response and anticipation of outcome, see Geier, et al., 2010). In such neuroimaging studies, responses to anticipated and received rewards are usually investigated using tasks in which participants can receive an outcome that is favorable to them. Outcomes can be points, money or primary rewards such as juice (Delgado, 2007). A consistent finding in these studies is involvement of the ventral striatum/nucleus accumbens in response to receipt of rewards. In addition, the amygdala, anterior cingulate cortex (ACC), dorsolateral prefrontal cortex (DLPFC), ventromedial prefrontal cortex (VMPFC) and orbitofrontal cortex (OFC) are also found to be active, although these findings are not consistent across studies and possibly depend on specific task demands. In this thesis the focus will be on the developmental pattern in the ventral striatum specifically, as this region is most consistently activated in response to reward anticipation and reward processing.

**Ventral striatum responses to reward**

The striatum is part of the basal ganglia complex. The striatum receives synaptic input from cortical and subcortical regions, such as dopaminergic input from the substantia nigra. The striatum can be subdivided into the dorsal and ventral striatum. The dorsal parts of the striatum primarily include the caudate nucleus and the putamen. The ventral striatum includes the nucleus accumbens, and ventral parts of the caudate nucleus and putamen. The ventral striatum receives input from pre-frontal regions such as the orbitofrontal cortex. The ventral striatum is a key region for reward processing (Delgado, 2007). In reward studies both under- and over recruitment of the ventral striatum have been reported in adolescents compared to children and adults. The most prominent finding is an over recruitment of the ventral striatum in response to reward receipt for adolescents. These results have been found with different tasks and in a wide age range, including participants between 7-40 years of age, strengthening the credibility of the results (Christakou, Brammer, & Rubia, 2011; Ernst, Nelson, Jazbec, McClure, Monk, Leibenluft, Blair, & Pine, 2005; Galvan, Hare, Parra, Penn, Voss, Glover, & Casey, 2006; Van Leijenhorst, Gunther Moor, Op de Macks, Rombouts, Westenberg, & Crone, 2010a; Van Leijenhorst, Zanolie, Van Meel, Westenberg, Rombouts, & Crone, 2010b).

The tasks used in these studies often involve an aspect of gambling, passive or active. Passive gambling refers to paradigms in which the participant cannot influence the outcome, whereas an active task means that the participant can choose to take a risk or not. Two studies with passive gambling tasks support the hypothesis of over recruitment of the ventral striatum to reward in adolescence. Van Leijenhorst et al. (2010b) used a task in which participants are shown a slot machine that they can start with a button press. The slots can fill with three types of fruit. Only when all three slots show the same fruit, they win. Winning was associated with increased activation in the ventral striatum, and more so for mid-adolescents. Similarly, Galvan et al. (2006) used a delayed response two-choice task. In this task, participants are presented with a cue, after which they need to respond by indicating the location of the cue when prompted. Correct responses within the time interval set for the response are rewarded. Each cue is paired with a distinct reward amount. Again, winning was associated with increased activation in the ventral striatum, with a peak in mid-adolescence.

Tasks with an active aspect of gambling, such as the wheel of fortune task (Ernst, et al., 2005) and the cake gambling task (Van Leijenhorst, et al., 2010a), similarly show greater activation of the ventral striatum in response to reward receipt. In the wheel of fortune task, participants are shown a circle divided into two colors. Only trials were analyzed in which both colors covered 50% of the circle in this case, but divisions and therefore probabilities of winning can differ. Participants choose one of the colors and if the computer randomly picks the same color, they win. The cake gambling task is a slightly modified version of the wheel of fortune task. To make the task more suitable for children, the wheel is explained as a cake with different flavors. Participants can choose which flavor they would like to bet on and if the computer picks the same flavor they win. Participants can choose between a low-risk gamble with a 66% chance of winning 1 euro, and a high-risk gamble with a 33% chance of winning 2, 4, 6 or 8 euros. In these tasks, winning was associated with increased activation in the ventral striatum. Striatum activation showed a peak in mid-adolescence. This pattern of elevated ventral striatum response in mid-adolescence was further confirmed in other paradigms which have used reward conditions, such as a temporal discounting task (Christakou, et al., 2011), an anti-saccade task (Geier, Terwilliger, Teslovich, Velanova, & Luna, 2010; Padmanabhan, Geier, Ordaz, Teslovich, & Luna, 2011) and a juice delivery paradigm (Galvan & McGlennen, 2013). Smith et al. (2011) used a sustained attention task in which adolescents showed elevated ventral striatum responses to rewarded trials compared to adults, but not compared to the youngest group. The results from this set of studies seem to provide consistent evidence for enhanced activation in the ventral striatum in mid-adolescence. However, in work focusing on the anticipation of rewards, the results of some studies have been opposite to the pattern described above. Two studies have found under recruitment of the striatum in mid-adolescence. Both of these studies used the Monetary Incentive

Delay (MID) task (Bjork, Knutson, Fong, Caggiano, Bennett, & Hommer, 2004; Bjork, Smith, Chen, & Hommer, 2010). In the MID task, participants can win (or avoid losing) different amounts of money by pressing a button within a short interval after a target is presented. Failure to press within the response interval results in omission of gain (or loss), whereas pressing the button within the response interval results in winning (or avoidance of loss).

As stated before, two general phases can be distinguished in reward paradigms; the anticipation of reward and the receipt of the reward (feedback). The apparent inconsistency of results might be a result of confounding anticipation of reward and receipt of reward. The MID task has two distinguished phases, separated in time to allow for fMRI analyses for both phases. As such it has been specifically designed to enable testing for differences in brain activation during anticipation, as well as receipt, of a reward. Both studies (Bjork, et al., 2004; Bjork, et al., 2010) found under recruitment of the right ventral striatum for adolescents, compared to an adult group, during gain versus non-gain anticipation. Activation during reward receipt, in contrast, did not yield any significant differences between the groups.

Taken together, the imbalance model proposed by Somerville et al., (2010) provides a framework to understand risk taking behavior. However, empirical studies testing this model have yielded mixed results. These mixed results could be due to small sample sizes and different task demands (for a review see Richards et al, 2013). In this thesis one of the aims is to test whether ventral striatum responses to rewards show hypo- or hyperactivity in adolescence. To test this a large sample with a continuous age range was used and participants were tested using a new paradigm to assess reward processing. Furthermore, the imbalance model does not specify which individual difference factors might be related to ventral striatum responses. In this thesis the aim is to obtain more information about the ventral striatum responses to reward and its specificity in adolescence, and to identify individual difference factors that are related to the ventral striatum response to rewards. Individual difference factors of interest in this thesis are chronological age, pubertal development, hormone levels, personality and social context.

**Pubertal hormones**

Since adolescents go through major changes in hormone levels as well as in the social domain, this leads to the hypothesis that hormonal and social contextual factors may influence developmental sensitivities in ventral striatum responses to rewards. These factors will be discussed below, starting with the influence of pubertal hormones.

The onset of adolescence coincides with the onset of puberty. Puberty is characterized by the development of secondary sexual characteristics, changes in behavior, accelerated growth and it eventually leads to reproductive capacity. Pubertal development occurs as a function of activation of the hypothalamic-pituitary-adrenal (HPA) and hypothalamic-pituitary-gonadal (HPG) axes. The HPG axis secretes gonadotropin-releasing hormone (GnRH) from the hypothalamus, luteinizing hormone (LH) and follicle-stimulation hormone (FSH) from the pituitary gland, and estrogen and testosterone from the gonads. Males and females both produce estradiol and testosterone, but in different ratios. Both testosterone and estradiol have an effect on the brain through androgen and estrogen receptors.

Puberty related hormonal changes do not only trigger reproductive development, but probably also influence social behaviors and interest in peers, such as sensation seeking, seeking of social status, fear of social rejection and a drive towards social acceptance (Dahl, 2004; Nelson, Leibenluft, McClure, & Pine, 2005). The association between testosterone and risk taking in adults has been mainly studied through the measurement of naturally fluctuating hormone levels, but recently, exciting new advances in testosterone research have focused on the administration of testosterone in healthy (mostly female) adult participants. Administering small doses of testosterone, compared to placebo, resulted in increased risk taking a gambling task (van Honk, Schutter, Hermans, Putman, Tuiten, & Koppeschaar, 2004). In addition, administration of the same dose of testosterone in females resulted in enhanced activation in the nucleus accumbens during reward anticipation in the MID task (Hermans, Bos, Ossewaarde, Ramsey, Fernandez, & van Honk, 2010). One study used a slightly different approach and investigated the effects of single dose testosterone administration on approach-avoidance behavior in young female adults (Enter, Spinhoven, & Roelofs, 2014). Testosterone administration was related to a relative increase in approach tendency of potentially threatening stimuli (angry faces). Higher approach tendency might partly explain a higher tendency to take risks.

The natural increase in testosterone during puberty is orders of magnitude larger than the increase due to administration of testosterone in the examples described above. Therefore, an intriguing question is whether hormone level increases are predictive of neural responses to risk and reward in pubertal adolescents. Two studies used this approach. A study by Op De Macks et al. (2011) found that boys and girls with higher natural testosterone levels also showed higher ventral striatum responses to reward receipt, thereby confirming prior studies which showed that testosterone administration in adults also leads to enhanced ventral striatal responses to reward (Hermans, et al., 2010). However, as described before, responses to reward anticipation and reward receipt may rely on different mechanisms. This is highlighted in a study by Forbes et al. (2010) in which testosterone levels correlated positively with striatum responses in boys during anticipation, but correlated negatively with striatum responses to reward receipt in both boys and girls.

Taken together, these studies provide the first evidence for a role of testosterone on ventral striatum activity to rewards. However, the exact link between the two is unclear. In this thesis this link is further investigated by relating testosterone levels to ventral striatum responses to reward.

**The influence of social factors on reward processing**

It is well known that peers have a large influence on the behavior of adolescents. Adolescence is a time when peers become very important (Dahl, 2004) and much risk taking behavior takes place in groups (Steinberg, 2004). When adolescents are asked to perform a task in the lab, they are usually alone or in the presence of an experimenter, not among their peers. The risk taking behavior that is observed in a natural setting may therefore not be captured in the standard laboratory environment. The influence of social factors on neural correlates of risk taking is a relatively new, but active area of research.

One of the first studies to use a social approach was an fMRI study investigating risk taking in a setting with peers for three age groups: adolescents, aged 14-18; young adults, aged 19-22 and adults, aged 24-29. In this study by Chein et al. (2011; see also Gardner & Steinberg, 2005), participants were asked to play a game in which they were driving a simulated car. Their goal was to drive from A to B as fast as possible. On the way, they encountered several crossings. On some of these crossings a stoplight turned orange, just when they approached. On each crossing they could decide to (continue to) go and take a risk, or stop. When they decided to take a risk, this could result in a crash, setting them back further than deciding to wait would have. In one condition, participants were told that they were performing this task alone and that no one would see what they did. In the other condition, however, their peers were physically present and watching them. All groups showed elevated risk taking in the peer-present condition, but adolescents took even more risks than young adults and adults. Intriguingly, adolescents also showed elevated ventral striatum responses in the peer present condition compared to the other age groups.

This initial study has been followed up with other studies showing similar results and this effect is now known as the 'peer effect'. To parse out relevant factors that contribute to the peer effect several follow-up studies have been done. Real life risk taking behavior often occurs under situations of unknown probabilities of negative outcomes (e.g. running a red light, cycling without a helmet). A study by Smith et al, 2014) showed that risk taking behavior is also influenced by peers in a situation in which the probabilities for winning and losing were explicitly provided. Participants who believed that they were observed by an unknown peer chose to gamble more often than participants who performed the task alone.

To investigate whether peer observation influenced impulsive choice behavior, two studies used a delay discounting paradigm (O'Brien, Albert, Chein, & Steinberg, 2011; Weigard, Chein, Albert, Smith, & Steinberg, 2014). In a delay discounting task participants are presented with the choice between a smaller, sooner or a larger, later reward. Higher proportion of choices for a smaller, sooner reward is indicative of more impulsive behavior. In one study participants were watched by two same age, same sex peers (O'Brien, et al., 2011) and in another study participants were watched by an anonymous peer (Weigard, et al., 2014). Participants in both studies showed an increased preference for smaller sooner rewards when observed by a peer. These results indicate that the peer effect is not restricted to friends, but is also seen when participants were observed by an anonymous peer.

Taken together, these studies show that peer observation increases risky choice behavior in adolescence. However, which aspects of the social context interact with reward processing is unknown. Crucial questions are whether ventral striatum responses are also elevated when thinking about peers and what properties of the peer (liked vs disliked) are essential to this effect. In this thesis I investigate the influence of social context on ventral striatum responses to rewards. More specifically, I assess whether neural responses to winning and losing money for friends and disliked others differs from neural responses to winning and losing for self.

**Real life risk taking**

As stated in the beginning of the introduction, adolescence is related to increases in risk taking behavior in real life. Examples of real life risk taking behavior are alcohol use, substance abuse and delinquency (Steinberg, 2004). Many of the changes in risk taking behavior are thought of as normative transitions in explorative behavior and sensation seeking. However, in some situations risk taking behavior can have adverse effects, such as in the cases of excessive alcohol consumption. One of the goals of adolescent risk taking research in the lab is to explain and possibly predict which adolescents are prone to take potentially dangerous risks in real life.

It has been hypothesized that the peak in risk taking behavior observed in real life during adolescence and the peak in nucleus accumbens activation in adolescence observed in experimental studies are related. Indeed, a relationship was found between nucleus accumbens activation in a reward task and the likelihood of engaging in risky behavior in the real world (Galvan, Hare, Voss, Glover, & Casey, 2007). Real world risk taking behavior is a complex construct and the literature on the relationship between nucleus accumbens activation and risk taking is sparse. This might indicate that nucleus accumbens activation is not the only factor, but that the interplay with other factors is important. Other factors that have been proposed to influence real life risk taking are pubertal development (Collado, MacPherson, Kurdziel, Rosenberg, & Lejuez, 2014) and social context (Chein, et al., 2011). The exact interplay between these factors and their contribution to risk taking behavior is currently unclear. In this thesis I investigate the link between pubertal development, neural responses to rewards and real life risk taking, in this case alcohol use.

**Longitudinal analysis**

The most used study design is a cross-sectional design. Cross-sectional studies are a type of correlational studies. In this type of design, variables are measured once and the relationship between these variables is assessed. In cross-sectional studies many variables can be measured at little extra cost and effort, making this an ideal design for many studies. Relationships between variables are correlational. If a certain study would find a relationship between hormone levels and neural activation in a specific region, it cannot be concluded whether hormone levels cause neural activation or whether neural activation causes hormone levels. In other words, the directionality between variables cannot be determined.

Longitudinal studies are optimized for testing directionality of relationships. In such a design a specific group, cohort, is tested multiple times and variables of interest are measured at each time point. Causal relationships between variables can be reliably tested. Cohorts are usually comprised of a homogeneous group, all aged 14, or all inhabitants of a certain region. In a strict longitudinal design with only one cohort it can take many years to collect all data, requiring patience and devotion from the researcher. Moreover, if participants drop out this poses serious problems for the data analysis.

Combining a cross-sectional and longitudinal design into one, an accelerated or cohort-sequential longitudinal design, creates a design in which the benefits of both types of design are used. In such a design a group of a broad age range is measured multiple times. This design is optimized for testing both between (cross-sectional) as well as within (longitudinal) changes and is sensitive to changes in individual difference measures.

**Objectives and approach**

In summary, adolescent risk taking is an important avenue for research due to the possible adverse effects. Adolescence is associated with major changes in hormonal levels, brain function and social environment. Previous research investigated these changes and the relationship with risk taking behavior with promising results. However, some major questions remain unanswered. The first question concerns development of striatum responses during adolescence. In this thesis it is tested whether striatum responses are hypo- or hyperactive in adolescence and how testosterone levels are related to striatum responses to rewards. The second question concerns the influence of social context. Previous studies have shown that peers influence risky decision-making and striatum responses. However, exactly which aspects of social context interact with reward processing, and how social brain regions respond to social context over development is unknown. The last question is how changes in pubertal development, brain function and social environment together influence real life risk taking. The chapters in this thesis are centered around these main questions.

To optimally dissociate between and within subject changes and investigate individual differences, data was collected from a large, cohort-sequential longitudinal study. In this study, called Braintime, 299 participants between 8-27 were measured twice with a two-year interval. A new task paradigm was developed, which was administered in the MRI-scanner on both time points. This task is optimized to not only investigate reward related neural responses, but also to investigate social factors. In this task, participants are told that the computer would flip a coin and they are asked to predict whether the computer would flip heads or tails. Participants could win and lose money for different beneficiaries. At the first time point they could win and lose money for themselves, their best friend and a disliked other. At the second time point, participants played the same task, but now they could win and lose money for themselves, their best friend and their mother.

**Outline of the chapters**

The first two empirical chapters describe cross-sectional data in which the new paradigm is validated. The aim of these chapters is to disentangle the influence of affective and social brain regions on reward processing for different beneficiaries. **Chapter 2** describes a study in which neural responses to rewards for different beneficiaries are investigated. In this study a sample of young adults, between 18-25, is used. In **Chapter 3** a study is presented in which the same gambling task is administered to a large sample of participants between 8-25 years of age. In this study the aim is to answer two questions. The first question is how reward related neural regions develop with age and the second question concerns the influence of social brain regions on reward processing.  Changes between and within subjects are the focus of **Chapter 4**. In this chapter I zoom in on reward related neural responses when playing for self. I describe longitudinal data and focus on the relationship between neural responses to rewards and age, pubertal development, testosterone level, and risk taking. The aim of this study is to investigate which individual difference variables are related to changes in neural responses to rewards. In **Chapter 5** the focus is on development of social brain regions. I describe longitudinal data for playing for self and for a friend. Neural responses when playing for a friend are compared with neural responses when playing for self, irrespective of outcome. The aim of this study is to describe developmental changes in responsiveness of social brain regions. In the last empirical chapter I aim to link real life risk taking behavior to neural responses to rewards. In **Chapter 6** it is investigated whether those participants who indicate higher alcohol use on a self-report questionnaire, are also the participants who have higher levels of testosterone and show higher responses to rewards for themselves in the gambling task. Finally, **Chapter 7** summarizes the results of the empirical chapters and discusses the findings in light of the objectives stated in the introduction.