Teens, Testosterone and Time:
Neural, Endocrinological and Contextual Correlates of Adolescent Impulsivity

Dissertation
zur Erlangung des akademischen Grades
doctor rerum naturalium (Dr. rer. nat.)
im Fach Psychologie

eingereicht an der Lebenswissenschaftlichen Fakultät der Humboldt-Universität zu Berlin

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Eingereicht am: 07.09.2017
Verteidigt am: 23.03.2018

Für Mama

Acknowledgements

First of all, I would like to thank my advisor Wouter van den Bos, who has been (and still is) a true role model for me. You are an excellent scientist with your heart in the right place and an outstanding humor (Kom op!). I am proud to be your first PhD student and I am very glad that I met you (and your wonderful family) and that I could learn from you. Thank you so much for your guidance and support throughout the last three years. Moreover, I would like to thank Ralph Hertwig, who gave me the opportunity to do my PhD at ARC, challenged me and thus taught me strength and endurance, which I am now very grateful for. I also want to thank Sam McClure, who introduced me into science. Without you, I would probably have never ended up where I am right now. Finally, I want to thank Tobias Kalenscher, whose passion and commitment during my master studies paved the way to my academic career.

I also want to thank all members of ARC, especially all my office mates during the last three years: Mattea, Sasha, Anika, Kyanoush, Peter, Philipp and Christina. Furthermore, I am grateful to be part of LIFE, where I met so many wonderful and interesting people, who always supported me in my research topic and gave me excellent and constructive feedback. Johanna, Sasa, Marty, Felix, Toni, Lena, Elisa – it has been great spending time with you during (and after) the seminars and the academies and I am very glad to also call you my friends. Many thanks must also go to ARC IT, especially Phillip (I am going to miss our therapy sessions), as well as Sonali Beckmann and Nadine Taube for helping me conducting the fMRI study.

Of course, I also have to thank my entire family, especially my father, who taught me the right values in life and constantly inspires me. I also want to thank my american mum Irene, who always encouraged me to achieve my very best in life. All of you always believed in me and gave me a lot of strength. I love you very much! Special thanks goes also to all my friends for their emotional support: Kiki and Sophie, my Transen Crew and Amina, the Göttingen Crew and last but not least, Lizzi and Perke (I am very glad that we found each other). Finally, I want to thank my better half and big love Oisin. Clearly, one of the best things that came out of this PhD is us. It is your invaluable support and love that made this possible. I finally found home.

Eidesstattliche Erklärung

Hiermit erkläre ich an Eides statt,

• dass ich die vorliegende Arbeit selbstständig und ohne unerlaubte Hilfe verfasst habe,

• dass ich mich nicht bereits anderwärts um einen Doktorgrad beworben habe und

keinen Doktorgrad in dem Promotionsfach Psychologie besitze, und

• dass ich die zugrundeliegende Promotionsordnung vom 3. August 2006 kenne.

Berlin, den 07.09.2017

Corinna Laube

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SUMMARY

Adolescence describes the developmental phase between childhood and adulthood and is characterized by rapid changes in physiology, hormones and behavior. Typical adolescent behavioral tendencies such as risk taking and impulsivity are thought to evolve from a major biological reorganization of the adolescent brain. However, it remains unclear how these large scale biological changes impact specific processes that result in increases in risky and impulsive decision-making in adolescence. The current dissertation aims at elucidating the cognitive, affective and neural mechanisms of adolescent impulsivity by 1) highlighting the role of puberty and 2) combining different levels of analyses, including cognitive or affective measures, with biological measures such as pubertal hormones and functional magnetic resonance imaging (fMRI), in combination with cognitive modeling techniques.

The dissertation is publication-oriented and consists of four pieces of work. At the time of submitting this dissertation, *Paper I* and *Paper II* have been published, and *Paper III* and *Paper IV* exist as complete drafts that have been submitted for publication. *Paper I* gives a general overview of the current state of the art on the relationship between pubertal hormones, affective processing and increased impulsive and risky decision-making in adolescence. It discusses findings of empirical studies focusing on both adolescent behavior and the brain in the light of pubertal maturation in humans and animals and formulates new research directions. The following three papers are empirical studies that tackle the questions made in *Paper I*, examining specifically *impatience*, which is defined as one subcomponent of the more broader construct of impulsivity (Romer, 2010). While each paper focuses on impatient decision-making, they differ in terms of the mechanism being investigated: *Paper II* focuses on puberty, in particular testosterone and its relationship to impatient decision-making. Consistent with previous studies, age, but not testosterone is associated with an overall decline in discounting in early adolescence, while testosterone but not age is associated with increased sensitivity to immediate rewards. *Paper III* investigates the neural

mechanisms underlying the relationship between pubertal testosterone and impatient decision-making previously described in *Paper II*. Here, results indicated that testosterone specifically impacts the dorsal, but not the ventral striatum, which in turn lead to behavior that was biased towards choosing smaller sooner rewards. Finally, *Paper IV* focuses on affective processing, specifically on how the affective content of a reward impacts impatient decision-making. In two independent studies, increased levels of positive affect were consistently associated with an increase in impatient decisions. The underlying mechanism that may explain this increased impatient behavior is a shift in time judgment.

In summary, this dissertation thoroughly investigated the underlying mechanisms of impatient decision-making by using a multimodal approach with measures of affect, fMRI, and hormonal assessment combined with cognitive modeling of task-related behavior. It extends previous findings on adolescent behavior and brain development by elucidating the role of pubertal hormones with regard to specific processes underlying impatient decision-making, both on a behavioral and neural level. Finally, it redefines the role of pubertal testosterone by proposing a novel framework that highlights its impact on executive control, thus offering novel, exciting directions for future research.

ZUSAMMENFASSUNG

Die Adoleszenz beschreibt die entwicklungspsychologische Phase zwischen der Kindheit und des Erwachsenenalters, die durch rapide Veränderungen in der Physiologie, im Hormonhaushalt und Verhalten charakterisiert ist. Typische jugendliche Verhaltenstendenzen wie risikohaftes Verhalten und Impulsivität werden einer erheblichen biologischen Umstrukturierung des jugendlichen Gehirns attribuiert. Unklar ist jedoch, wie sich diese massiven biologischen Veränderungen auf spezifische Prozesse auswirken, welche in ein erhöhtes risikohaftes und impulsives Entscheidungsverhalten in der Adoleszenz resultieren. Die vorliegende Dissertation setzt sich zum Ziel, die kognitiven, affektiven und neuronalen Mechanismen der jugendlichen Impulsivität zu untersuchen. Hier wird der Pubertät eine besondere Rolle zugeschrieben und unterschiedliche Analyseebenen wie kognitive und affektive Maße mit biologischen Maßen wie Hormonen kombiniert, sowie Methoden der funktionellen Magnetresonanztomographie (fMRT) und kognitiven Modellierung angewandt.

Die vorliegende Dissertation ist publikationsorientiert und besteht aus vier Projekten. Zum Zeitpunkt der Abgabe der Dissertation sind *Kapitel I* und *Kapitel II* erschienen, und *Kapitel III* und *IV* sind als vollständige Manuskripte bei unterschiedlichen peer-reviewed Journals eingereicht.

Kapitel I gibt eine generelle Übersicht zum aktuellen Forschungsstand über den Zusammenhang zwischen Hormonen in der Pubertät, affektiver Verarbeitung und erhöhter Impulsivität und Risikobereitschaft in der Adoleszenz. Es werden Befunde von empirischen Studien mit Menschen und Tieren diskutiert, welche sich mit jugendlichen Verhalten, sowie Gehirnentwicklung während der Pubertät befassen, sowie zukünftige neue Forschungsschwerpunkte formuliert. Die folgenden drei weiteren Kapitel sind empirische Studien, welche sich mit den offenen Punkten aus dem ersten Kapitel befassen. Alle drei Studien untersuchen Ungeduld, da diese als eine spezifische Subkomponente von dem eher allgemein gefassten psychologischen Konstrukt der Impulsivität definiert ist (Romer, 2010).

Während sich alle drei Studien auf die ungeduldige Entscheidungsfindung fokussieren, entscheiden sie sich dennoch in den untersuchten Mechanismen: *Kapitel II* fokussiert sich auf die Pubertät, speziell auf Testosteron und seinen Zusammenhang mit ungeduldiger Entscheidungsfindung. Konsistent mit früheren Studien ist das chronologische Alter (und nicht Testosteron) assoziiert mit einer generellen Abnahme der Diskontierung in der frühen Adoleszenz, während hingegen Testosteron (und nicht das Alter) mit einer erhöhten Sensitivität für sofortige Belohnungen einhergeht. *Kapitel III* untersucht die neuronalen Mechanismen, die der Beziehung zwischen Testosteron in der Pubertät und ungeduldigem Entscheidungsverhalten (dargestellt im vorherigen zweiten Kapitel) unterliegen. Ergebnisse dieser Studie zeigen, dass Testosteron in der Pubertät speziell das dorsale, nicht jedoch das ventrale Striatum beeinflusst, welches mit der Entscheidung für kleinere, aber zeitlich früherer Belohnungen einhergeht. Die letzte Studie in *Kapitel IV* befasst sich mit der Frage, wie der affektive Inhalt einer Belohnung ungeduldige Entscheidungsfindung beeinflusst. Zwei unabhängige Studien haben gezeigt, dass erhöhte Levels an positiven Affekt mit einer Zunahme an ungeduldigen Entscheidungen assoziiert waren. Ein möglicher Mechanismus, der dieses Ergebnis erklären kann, ist eine Veränderung der Zeitwahrnehmung.

Zusammenfassend untersucht die vorliegende Dissertation in sehr umfangreicher Art und Weise die zugrundeliegenden Mechanismen von ungeduldiger Entscheidungsfindung und kombiniert in einem multi Modell Ansatz Maße von Affekt und Hormonen mit Methoden, wie der fMRT und kognitiver Modellierung von aufgabenbezogenen Verhalten. Ergebnisse früherer Studien über jugendliches Verhalten und Gehirnentwicklung werden durch die vorliegende Doktorarbeit erweitert, indem Hormone in der Pubertät eine besondere Hervorhebung genießen und in diesem Zusammenhang spezifische Prozesse, die der impulsiven Entscheidungsfindung unterliegen, auf neuronaler und verhaltensbasierter Ebene umfangreich und sorgfältig analysiert werden. Schließlich wird die Rolle von Testosteron in der Pubertät neu definiert und es wird ein neues Framework vorgeschlagen, welches den

Einfluss von Testosteron auf die kognitive Kontrolle in der Pubertät besonders hervorhebt und somit neuartige, spannende Ideen für die zukünftige Forschung darbietet.

LIST OF ORIGINAL PAPERS

Paper I

Laube, C. & van den Bos, W. (2016). Hormones and Affect in Adolescent Decision Making. In S. Kim, J. Reeve & M. Bong (Eds*), Recent Developments in Neuroscience Research on Human Motivation (Advances in Motivation and Achievement, Volume 19)*(pp.259-281)*. UK:Emerald Group Publishing Limited. doi:10.1108/S0749-742320160000019013

Paper II

Laube, C., Suleiman, A. B., Johnson, M., Dahl, R. E., & van den Bos, W. (2017). Dissociable effects of age and testosterone on adolescent impatience. *Psychoneuroendocrinology*, *80*, 162–169. doi:10.1016/j.psyneuen.2017.03.012

Paper III

Laube, C., Lorenz, R. & van den Bos, W. (under review). Pubertal Testosterone Correlates with Adolescent Impatience and Dorsal Striatal Activity. *Nature Neuroscience*.

Paper IV

Laube, C. & van den Bos, W. (under review). It's About Time: How Integral Affect Increases Impatience. *Emotion.*

LIST OF ABBREVIATIONS

ADHD   Attention Deficit Hyperactivity Disorder

BART   Balloon Analogue Risk Task

DHEA   Dehydroepiandrosterone

DLPFC   Dorsolateral Prefrontal Cortex

fMRI   functional Magnetic Resonance Imaging

NAcc   Nucleus Accumbens

PDS   Pubertal Developmental Scale

ROI   Region of Interest

WHO   World Health Organization

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1. Introduction

"Ich bin, aber ich habe mich nicht, darum werden wir erst". (Ernst Bloch, 1945).

Around 1 in 6 people in the world is an adolescent; totaling 1.2 billion people aged 10 to 19 (WHO, 2017). Adolescence describes the developmental phase between childhood and adulthood. It is a time of many physical, cognitive and social-emotional changes (Crone & Dahl, 2012) and is characterized by a transition from dependency to independency, as well as sexual maturation. This path to independence bears both challenges and opportunities, where the individual has to find her way towards being an independent actor in society (Blakemore & Robbins, 2012). Referring to Bloch's quote above, one may interpret that it is exactly this missing feeling of identity that is driving adolescents to explore the world and explore themselves in order to reach the final goal of becoming an adult and leading an independent life. Clearly, puberty, which represents the onset of adolescence, is distinguished by large scale and rapid physical and mental changes, representing a challenging time to establish a continuous identity. As such, adolescence is a phase of major social re-orientation, where the teenager begins to orient herself towards the mindset of like-minded peers and away from the influence of parents (Nelson, Leibenluft, McClure, & Pine, 2005; van den Bos, 2013). Being an adolescent also means more freedom and autonomy in choosing with whom and how to spend your time compared to when being a child. In addition, one salient characteristic of adolescence is an increase in risky and impulsive behavior (Braams, van Duijvenvoorde, Peper, & Crone, 2015; O'Brien, Albert, Chein, & Steinberg, 2011; Steinberg et al., 2009). Social problems in adolescence such as substance abuse, drunk driving, suicide, and teenage pregnancy are often attributed to this increased risk taking and impulsivity (Dahl, 2004). As a consequence, one may argue that it is the unique combination of newly gained autonomy and

increased impulsive and risk-taking behavior that bears the potential risk of negative health and social outcomes. For instance, an estimated 1.3 million adolescents died in 2015, mostly from preventable or treatable causes (WHO, 2017). Furthermore, criminal behavior shows a rise in adolescence and a decline in young adulthood (Shulman, Steinberg, & Piquero, 2013). Nevertheless, impulsivity in adolescence clearly also serves an adaptive function, making it possible for the individual to eventually become an independent actor in society (Spear, 2000). Thus, the challenge is to support healthy development in adolescence by leaving enough room for impulsive behavior, while at the same time minimizing its risks. In order to do so, a better understanding of the underlying mechanisms driving impulsive behavior in adolescence is essential.

Recent research emphasizes *puberty* as a key maturational window for risky (Braams et al., 2015; Cardoos et al., 2017) and impulsive behavior (Laube, Suleiman, Johnson, Dahl, & van den Bos, 2017). Puberty is a cross-species and cross-cultural biological phenomenon and has been associated with changes in social and affective processing (Crone & Dahl, 2012; Forbes & Dahl, 2010). In particular, it has been hypothesized that pubertal hormones specifically impact motivational processes during adolescence, which in turn lead to increased risk taking and impulsive behavior, but also support positive development (Crone & Dahl, 2012). However, little is known about the mechanisms that mediate the relationship between pubertal hormones and changes in motivational processes during adolescence or how these changes in motivational processes may heighten adolescent risk taking and impulsivity.

In my dissertation, I aim at shedding more light onto these questions by using a multimodal approach, with a specific focus on impatience, as part of the multidimensional construct of impulsivity. *Paper I* gives a general overview of the current state of the art on the relationship between pubertal hormones, affective processing and increased impulsive and risky decision-making in adolescence. The following three papers are empirical studies that tackle the open points made in the review paper. While each paper focuses on impatient

decision-making, they differ in terms of the mechanism being investigated: *Paper II* focuses on puberty, in particular how testosterone is related to impatient decision-making. *Paper III* investigates the neural mechanisms underlying the relationship between pubertal testosterone and impatient decision-making, previously described in *Paper II*. Finally, *Paper II* focuses on affective processing, specifically on how the affective content of a reward impacts impatient decision-making.

First, I shortly outline the theoretical and empirical background of my dissertation. Following this, I give a short summary of each of the papers included in this dissertation. Finally, the results of my dissertation are discussed, considering limitations as well as future research directions.

2. Theoretical and Empirical Foundations

2.1 Decision-making in Adolescence

The notion that adolescence is a "specific" period characterized by turbulent and irrational behavior is not a modern concept, but dates back already to ancient Greece. As Aristotle once stated "youth are heated by nature and drunken men by wine" (citation from Dahl, 2004), teenagers' shortcomings such as rashness, sexual excess, frivolity, drunkenness and lack of self-control were also portrayed in ancient Greek art (Harlow & Laurence, 2002). This sentiment remains in place until today, where problematic adolescent behavior is a core topic of societies' concerns, reflected in the media, as well as literature. Social problems, such as drunk driving, suicide, depression and teenage pregnancies are attributed to increased risk taking and impulsivity in adolescence. Eventually, this "outlandish behavior" results in significant increase in visits to the emergency room, leading to a 200% increase in mortality rate among teenagers (Dahl, 2004).

However, there exists a discrepancy between the stereotypical impulsive teenager in the real world and adolescent behavior studied in the laboratory. A recent study by van den Bos and colleagues (2015) showed a decrease in impulsivity as age increases, suggesting that teenagers are not necessarily more impulsive than children and rather follow a normal trajectory between childhood and adulthood. Several other studies reported the same linear association between impulsivity and age, showing that children are more impulsive than adolescents (Prencipe et al., 2011; Scheres et al., 2006) and adolescents are more impulsive than adults (Olson, Hooper, Collins, & Luciana, 2007; Steinberg et al., 2009). This finding is in line with decades of research on cognitive control, supporting a steady improvement of cognitive control abilities during adolescence (Asato, Sweeney, & Luna, 2006; Huizinga, Dolan, & van der Molen, 2006). Moreover, the transition from childhood to adulthood is characterized by a significant improvement in cognitive processing speed and intellectual

functioning, specifically with respect to executive functions such as abstract thinking, response inhibition, attentional control and memory capacity (Rosso, Young, Femia, & Yurgelun-Todd, 2004). Hence, at least some cognitive processes follow a linear trajectory in adolescence, meaning that transitional changes continue to show a steady increase or decrease from childhood to adulthood, resulting in adolescent-nonspecific processes. However, this linear improvement in executive functioning, specifically in cognitive control, cannot explain the observed peak in impulsive behavior in adolescence often seen in the real world. Importantly, a study by Scheres and colleagues (2014) also reported non-linear age-related differences in impulsive behavior, with adolescents showing less impulsivity compared to children and adults. Yet another study reported no differences between adolescents and adults (Audrain-McGovern et al., 2009). Clearly, inconsistencies exist in the literature, which a model solely based on executive functioning is not able to explain.

Likewise, there are inconsistent results for age-related differences in the risky decision-making literature. While several studies report a linear decline in risk behavior with age, with adolescents showing less risky decision-making than children (Crone & van der Molen, 2007; Hooper, Luciana, Conklin, & Yarger, 2004) and more than adults (Mitchell, Schoel, & Stevens, 2008; Van Duijvenvoorde, Jansen, Bredman, & Huizenga, 2012), other studies did not report any differences between adolescents and adults (Cauffman et al., 2010; Overman et al., 2004). Yet, other studies showed evidence for non-linear age-related differences, with adolescents peaking in risky decision-making compared to both children and adults (Burnett, Bault, Coricelli, & Blakemore, 2010; Smith, Xiao, & Bechara, 2012). A recent meta-analysis by Defoe and colleagues (2015) demonstrates this inconsistency in the literature and thus reveals a discrepancy between patterns of risk-taking in the real world and adolescent behavior as studied in the laboratory. One possible reason for this discrepancy is that the structure of the tasks used in laboratory studies does not match that of the real-world environment, particularly in terms of affective content.

Interestingly, a handful of studies in the context of risk have shown that the affective loading of the decision moderates adolescents' risk appetite. Although adolescents are more likely than children or adults to make risky choices in emotionally charged or "hot" contexts, in low-affect or "cold" tasks, adolescents seem to show levels of risk taking similar to those of adults (Crone & van der Molen, 2007; Hooper, Luciana, Conklin, & Yarger, 2004). Similarly, for impulsive decision-making, a study by O'Brien and colleagues (2011) found that adolescents preferred more immediate rewards to later ones when in the presence of their peers. In this study, participants had to choose between a smaller sooner reward (e.g., $200 today) and a larger later reward (e.g., $1,000 in one year). Adolescents were more likely to choose the smaller sooner reward in the presence of peers than when alone. The presence of peers is hypothesized to be a highly arousing context for adolescents and this increased arousal is thought to change their behavior in a similar fashion as the arousing context provided by "hot" gambling games.

Crone and Dahl (2012) highlight the motivational salience of the context and propose a flexible cognitive control model in adolescence. That is, the extent to which cognitive control systems are recruited might be influenced by factors such as peer presence, task instructions or the affective appraisal of value (Defoe et al., 2015). Consequently, studying the interactions between cognitive and affective systems and their individual and distinct developmental trajectories is a fruitful and promising approach for better understanding the adolescent-specific peak in risky and impulsive behavior.

2.2 Neurodevelopmental models of adolescent brain development

According to previous models of adolescent brain development, increased impulsive behavior in adolescence may be explained by a maturational gap between cognitive control and affective processes (Casey, Getz, & Galvan, 2008; Steinberg, 2010). In accordance with these models, a relatively faster maturation of subcortical affective brain areas in comparison to

more slowly maturing frontal cortical brain areas may serve as an explanation for adolescent behavior that ignores long-term outcomes and thus seems to be more emotional or less rational. Notably, although all models predict that the subcortical affective brain areas develop early in adolescence, evidence has been mixed. Some studies have reported that the ventral striatum, a crucial region in the brain's reward circuitry, shows peak activity in adolescence (Braams, Peters, Peper, Güroğlu, & Crone, 2014; Galvan et al., 2006), while others have found no such evidence (Bjork, 2004; Bjork, Smith, Chen, & Hommer, 2010; Richards, Plate, & Ernst, 2013). Particularly, most studies focused exclusively on chronological age, which may be a possible reason for conflicting results. Importantly, recent research suggests that a more nuanced understanding of interactions across cognitive, affective and social processing is required (Pfeifer & Allen, 2012). Currently there is a renewed interest in the role of pubertal hormones (Blakemore, Burnett, & Dahl, 2010; Crone & Dahl, 2012; Forbes & Dahl, 2010; Peper & Dahl, 2013). However, chronological age is not a reliable predictor of pubertal status. Data from a five-year longitudinal study reported a considerable degree of individual differences in pubertal onset, ranging from 8.0 to 14.9 years in females and from 9.7 to 14.1 years in males and is complete by 12.4 to 16.8 years in females and by 13.7 to 17.9 years in males (Lee, 1980). Thus, it seems likely that many studies with a focus on chronological age have failed to detect pubertal changes in reward behavior and related brain activity.

2.3. Pubertal development

Pubertal development is characterized by a rapid rise in gonadal hormone release initiating development of secondary sexual characteristics, such as breast development in girls and pubertal hair growth, as well as other physiological changes like physical growth. Sex hormones regulating bodily changes are testosterone, oestradiol, and dehydroepiandrosterone (DHEA). Both internal and external cues provide information on the availability of the

resources required for fruitful reproduction, thereby triggering puberty. Internal cues include metabolic levels of insulin, glucose, and leptin indicating somatic growth and metabolic fuel availability; e.g. lower body fat has been associated with delayed pubertal onset (Frisch, 1984). External cues include information on the availability of food and of a suitable mate. A common way of measuring external pubertal status is the Pubertal Developmental Scale (PDS) (Petersen, Crockett, Richards, & Boxer, 1988). The PDS asks adolescents about pubic hair growth, skin changes, and growth spurts, with sex-specific items, such as menarche and breast development in females and genital growth and facial hair in males. The resulting composite puberty score represents the effects of adrenal and gonadal hormones as well as growth hormones. Shirtcliff and colleagues (2009) investigated the interrelations of multiple measures of puberty and found that PDS scores are related to levels of basal hormones, such as testosterone in boys. Yet, even the best measure of external pubertal status captures less than half of the variability in basal hormones (Shirtcliff et al., 2009). Thus, measuring hormone levels in saliva or blood gives important insights into pubertal maturation that are not available from overt physical measures alone.

Although puberty is a cross-species, cross-cultural phenomenon (Spear, 2010) and thus represents a fruitful approach for understanding biological elements of adolescent behavior, research is scarce about how pubertal development impacts behavior in adolescence. There are only a handful of studies that report a positive relationship between pubertal testosterone and self-reported (Vermeersch, T'Sjoen, Kaufman, & Vincke, 2008) and behavioral risk-taking (Cardoos et al., 2017; Forbes et al., 2010; Peper, Koolschijn & Crone, 2013; Op de Macks et al., 2011). However, it is not known how pubertal testosterone is impacting impatience. Furthermore, the neural mechanisms underlying a possible relationship between pubertal testosterone impatience and risky behavior in adolescence are unclear. Yet, studying these relationships may resolve current issues in the field, such as the previously reported inconsistent findings in increased reward sensitivity in adolescence.

2.4. Open research questions

While the stereotypical teenager in the real world is described as impulsive and risk taking, recent research is inconsistent about this observation. When precisely reviewing the literature, it turns out that this increased impulsive and risky behavior is particularly apparent in *affective* contexts. Recently, it has been hypothesized that pubertal hormones play an important role in adolescent motivated decision-making (Blakemore, Burnett, & Dahl, 2010; Crone & Dahl, 2012; Forbes & Dahl, 2010; Peper & Dahl, 2013). However, scientific evidence is sparse, specifically with regard to task-related behavior. In addition, the cognitive, affective and neural mechanisms are not known. The current dissertation aims at elucidating the relationship between pubertal hormones and impatient decision-making in adolescence. To this end, an intertemporal choice paradigm was employed in order to measure impatience.

2.5 Intertemporal choice: A measure of impatience

The current dissertation focuses on a specific component of impulsivity, namely impatience. Impatience is often measured using a delay discounting paradigm that can measure differences in preference for delayed rewards (Ainslie, 1975; Frederick, Loewenstein, & O'Donoghue, 2002). Specifically, it is well known that future outcomes are discounted, or undervalued, relative to immediate ones. Put differently, the subjective value of a reward is known to decrease with increasing delay. The extent to which future outcomes are discounted has been shown to correlate with different real world outcomes such as earnings, education, early death in adolescence, substance abuse and pathological gambling (Bickel, Odum, & Madden, 1999; Golsteyn, Grönqvist, & Lindahl, 2014; Petry, 2001; Reimers, Maylor, Stewart, & Chater, 2009). Investigating delay discounting in developmental populations is of particular interest, since impatience is thought to result mainly from a lack of self-control, a characteristic attributed to children and adolescents. For instance, the most famous example of a one shot delay discounting task is the Marshmallow task by Mischel, Shoda and Peake

(1988). Here, children as young as 4 years were presented a marshmallow and were instructed to wait an unspecified time without eating the marshmallow to receive 2 marshmallows (until the experimenter came back into the room). While this task differs from the one used in the current dissertation in many ways, it nicely describes the essence of an *intertemporal* choice, where the individual has to choose between a smaller, but sooner and a larger, but later reward.

Recent research suggests that multiple cognitive and neural processes underlie delay discounting. One the one hand, increased impatience can result from an oversensitivity towards immediate options. For instance, literature suggests that people are more impatient when an immediate reward is present, compared to when both options are in the future (Loewenstein & Prelec, 1992). One the other hand, more patient behavior may result from processes such as contextual cues or priming, that bias attention away from immediate rewards or put emphasis on the importance of future goals. As an example, there exists evidence that an explicitly instructed future orientation leads to reductions in temporal discounting rates (Lempert & Phelps, 2016). While most developmental studies investigating impatience do not differentiate between these two distinct processes (except, to my knowledge, only van den Bos and colleagues (2015) and Steinbeis and colleagues (2016)) the current dissertation mainly focuses how these two distinct mechanisms underlying impatience contribute to developmental differences in adolescence. Most importantly, neuroimaging studies have consistently shown that delay discounting recruits distinct corticostriatal circuitry (Peper et al., 2013; Peters & Büchel, 2011; van den Bos, Rodriguez, Schweitzer, & McClure, 2014), which represent the main regions identified in neurodevelopmental models of adolescent brain development.

2.6 The Affect Gap

As previously summarized, affective processes seem to be of particular interest when trying to understand typical adolescent behavior. Interestingly, studies in young adults also provide evidence for a role of affect in decision-making, specifically in risky choice (Buechel, Zhang, Morewedge, & Vosgerau, 2014; Pachur, Hertwig, & Wolkewitz, 2014; Rottenstreich & Hsee, 2001). These studies suggest that in an affect rich context people focus on outcomes and pay less attention to probability information. Here, an affect rich context is operationalized via more real-world, highly arousing rewards, such as amenities of a vacation packages or kisses from your favorite movie star. Given the high real-world relevance of the stimuli used in this paradigm, it serves as a suitable task to test the hypothesis whether it is really the affective nature of either the situation being tested or of the options being evaluated that is driving impulsive behavior in adolescence. Nevertheless, before being able to test the hypothesis if developmental differences in impulsivity may be related to affect, there was a need for this paradigm originally developed by Pachur and colleagues (2014) to first be translated into the temporal domain (as it was based on risky choice) and test if young adults would indeed show increased impulsive choice for affect rich outcomes (as shown by Kim & Zauberman, 2013) as opposed to affect poor outcomes such as monetary rewards – termed as the affect gap. The study in *Paper IV* was set up to explicitly test this assumption in a modified version of an intertemporal choice task that is commonly used to assess impatience in both developmental and individual samples. In addition, we also aimed at elucidating the mechanisms underlying a possible affect gap in intertemporal choice.

3. Aims of Dissertation

Given the theoretical and empirical foundations described in the previous section, I pursue the following research goals:

1. Pubertal development is an understudied, yet powerful approach for understanding elevated levels of risky and impulsive behavior in adolescence. Therefore, I assessed the current state of knowledge on risk taking and impulsivity in adolescence and formulated predictions and suggestions for future research. Specifically, I outline how studying the effects of pubertal hormones on both behavior and brain may provide novel insights into understanding the underlying mechanism driving behavior in adolescence.

2. In order to investigate the underlying mechanisms of intertemporal choice in adolescence, I combined measures of salivary testosterone and self-reported pubertal status with detailed cognitive modeling of decisions on a curated set of intertemporal choices. I investigated potential dissociable effects of pubertal testosterone and age on adolescent impatience, by testing the hypothesis that an oversensitivity towards immediate rewards would be related to testosterone, while a decline in impatience across adolescence would be related to increasing age.

3. To add an additional layer of description and thus deeper understanding of the underlying mechanism of pubertal testosterone on impatience, I used a multimodal approach combining measures of fMRI, hormonal assessment and cognitive modeling of task-related behavior to investigated the neural correlates of salivary baseline testosterone on intertemporal choice, with a specific focus on the dorsal and ventral striatum.

4. Since affective processing is thought to be one mechanism explaining increased impatience in adolescence, I modified a paradigm that systematically compares impatient choice for relatively affect rich compared to relatively affect poor outcomes. Specifically, I tested the prediction that integral affect may explain increased impatient choice via context dependent changes in future time perception using two distinct samples of young adults.

4. Overview of Papers

The present dissertation is based on four pieces of work. *Paper I* summarizes evidence of increased risk-taking and impulsivity in adolescence within the framework of pubertal development and affective processing. In particular, it describes current open questions in the field and highlights pubertal status as measured by testosterone to play an important role when trying to enlighten the biological mechanisms contributing to impulsivity in adolescence. *Paper II* focuses on distinct effects of age and pubertal testosterone on adolescent impatience, whereas *Paper III* builds on the findings of *Paper II* by investigating the neural mechanisms underlying this relationship, specifically focusing on pubertal testosterone and impatience. Finally, *Paper IV* is concerned with the role of integral affect in impatient decision-making and aimed at modifying a traditional intertemporal choice paradigm to include rewards more relevant to adolescents and young adults.

Paper I

In this review paper we summarize evidence on risk-taking and impulsivity in adolescence and propose potential explanations by focusing on pubertal development and affective processing. We specifically focus on pubertal testosterone and relate reports to findings in the animal literature in order to further point towards potential neural mechanisms. The paper ends with recommendation for future research, highlighting the need to integrate measures of pubertal development, as well as affect, when trying to understand the mechanisms underlying impulsivity in adolescence.

Main Themes of Content

First, we summarize evidence from self-report and behavioral studies on adolescent decision-making in order to better understand the changes that occur in affective processing during adolescence and how those changes are related to a specific subset of behaviors: risk taking and impulsivity. Importantly, the current literature shows a discrepancy between adolescent risk taking the in the real world as opposed to studies in the laboratory, highlighting mixed findings for a peak in risk taking in adolescence (Defoe et al., 2015). By throughly examining and summarizing paradigms used in studies to investigate risky and impulsive behavior in adolescence, we identify a pattern of evaluated levels of these behaviors that is related to the affective content of the situation. In other words, there exists substantial evidence that adolescents show increased risk taking and impulsivity in laboratory studies under *arousing*

conditions. Thus these findings suggest that there is something specific about how adolescents process the affective motivational components of the tasks.

Because behavioral studies can provide only limited insights into the underlying mechanisms, we consider the role of pubertal development and argue that the motivational processes described above are specifically modified by hormones released during puberty. We briefly outline the biological mechanism behind hormonal changes seen in puberty and describe different methods used to assess pubertal development. Next, we review the literature on the influence of pubertal testosterone on adolescent behavior and conclude that testosterone has a sizeable influence on risky and impulsive behavior in adolescence, which is accompanied by context-dependent changes in motivational processing. Put differently, findings suggest a link between changes in motivational processing and changes in pubertal hormones.

We then turn to recent models of adolescent brain development and neurodevelopmental literature as they may provide useful insights into the mechanisms underlying the previously described relationship between changes in pubertal hormones and changes in motivational processing, which in turn may explain context dependent, elevated risk taking and impulsivity in adolescence. We present current models of adolescent brain development, which conjointly are based on the assumption of an imbalance between a cortical control network and a subcortical motivational network. In particular, it is hypothesized that prefrontal control areas mature slower than subcortical limbic structures, thus leading to unregulated or risky behavior, "like driving a car with a sensitive gas pedal and bad brakes" (Steinberg, 2014). Nevertheless, there exists quite some inconsistencies about whether limbic areas reach their peak in activity in adolescence, with studies showing that the ventral striatum is higher activated in response to rewards compared to children and adults (Braams et al., 2014; Galvan, Hare, Voss, Glover, & Casey, 2007), while others studies could not replicate such an effect (Bjork et al., 2010; Richards et al., 2013).

We propose that one possible reason for the mixed findings is that most studies focused on age rather than using direct measures of pubertal status. Given the pronounced variability in pubertal onset, it seems likely that many studies with a focus on chronological age have failed to detect pubertal changes in motivational behavior and related brain activity. Interestingly, studies including pubertal status have conjointly reported that pubertal testosterone predicts reward-related behavior.

For instance, Braams and colleagues. (2015) tested $N = 299$ participants at multiple time points and found that the average developmental trajectory of nucleus accumbens (NAcc) activation, an area crucial for reward processing, showed an inverted U-shape pattern. Moreover, they also found that changes in NAcc activation were positively correlated with changes in pubertal testosterone. This finding is in accordance with previous research reporting a relationship between pubertal testosterone and ventral striatum activity (Forbes et al., 2010; Op de Macks et al., 2016; Op de Macks et al., 2011).

Yet, what is still unclear is how pubertal hormones lead to changes in striatal activity. Therefore, we next turn towards animal studies, as puberty is not specific to humans but is a cross-species phenomenon (Spear, 2004). Notably, the animal literature highlights a role for testosterone in the dopamine system and reports evidence of adolescence-specific changes in dopamine pathways. We briefly describe two major pathways of dopamine projections in the brain, including the mesocorticolimbic dopamine system, which is associated with reward, learning, and motivation and the nigrostriatal dopamine system, where dopamine neurons primarily project to the dorsal striatum, associated with both goal directed and habitual behavior (Burton, Nakamura, & Roesch, 2015). A study by Stamford (1989) found reduced basal dopamine levels in the nigrostriatal pathway in periadolescent rodents, yet their dopamine storage pool was still larger compared to adults. Interestingly, Laviola and colleagues (2001) reported higher dopamine release in adolescents than in adult rodents, but only in rewarding contexts, suggesting that the high amount of potential dopamine release is

context dependent. Furthermore, gonadal hormones are thought to modulate dopamine signaling and thus play an important role in regulating adolescent developmental changes in the dopamine system (Sinclair, Purves-Tyson, Allen, & Weickert, 2014). Thus, we thoughrouly review studies including gonadectomy (the surgical removal of testes or ovaries) or experimental augmentation of testosterone, which consistently show multi-faceted effects on dopamine functioning with various behavioral consequences (Laviola, Macrì, Morley-Fletcher, & Adriani, 2003). Specifically, testosterone has differential effects across dopaminergic pathways, such as increasing dopamine neurotransmission in the substantia nigra (Purves-Tyson et al., 2014) and decreasing dopamine levels in the dorsal striatum (Matthews, Bondi, Torres, & Moghaddam, 2013; Purves-Tyson et al., 2014).

We next propose practical implications. Here, we highlight the importance of considering the teenagers' environment as a potential target for interventions rather than the teenager themselves. In other words, when trying to reduce maladaptive behaviors in adolescents, we think that it is crucial that interventions should match teenagers' biological developmental state and capabilities instead of actively teaching them to think differently.

Recommendations for Future Work

We end the paper with a short summary and future directions. To this end, I would like to emphasize that up until now,

> there is a lack of research that specifically (1) tests the relationship between pubertal hormone levels and risky and impulsive behavior in adolescence; (2) investigates the impact of pubertal hormone levels on brain regions associated with motivational processing; (3) describes how the relationship between pubertal hormones levels and brain regions changes over time; and (4) explains how this change is linked to developmental changes in risk taking and impulsivity. To address these questions, we propose the following directions for future research into pubertal effects on behavior

and brain functioning: First, studies should apply measures of pubertal age, ideally hormonal, as well as assessing chronological age. Second, the integration of different levels of analysis is essential. Studies that combine measures of behavior, its neural correlates, and how they interact with pubertal hormones such as testosterone in specific contexts are needed. Third, and most importantly, assessments at multiple time points are needed to capture intraindividual change over time. Longitudinal studies of development are imperative and can provide insights into interactions early versus late in puberty. Finally, gender differences must be considered, and hormones other than testosterone that undergo rapid changes during adolescence should also be investigated (e.g., estradiol and oxytocin).

In summary, investigating developmental changes on a hormonal level and focusing on neurotransmitters such as dopamine in the human adolescent brain is a promising avenue for gaining further insights into the specific neurobiological mechanisms underlying risky and impulsive behavior in adolescence. (Laube & van den Bos, 2016, p. 274-275)

Paper II

Laube, C., Suleiman, A. B., Johnson, M., Dahl, R. E., & van den Bos, W. (2017). Dissociable effects of age and testosterone on adolescent impatience. *Psychoneuroendocrinology*, *80*, 162–169. doi:10.1016/j.psyneuen.2017.03.012

In this paper, we investigated the dissociable effects of pubertal testosterone and age on impatient decision-making in *N* = 72 adolescent boys in a fairly small age range of 11-14 years. In order to get a precise description of these relationships, we used cognitive modeling to further distinguish the processes of sensitivity towards near-term rewards and general discounting of future options, which are both mechanisms underlying impatient behavior.

Theoretical background

Numerous self-report and behavioral studies support the characterization of the stereotypical impulsive teenager (Quinn & Harden, 2013; Steinberg et al., 2009; van den Bos et al., 2015). While impulsivity in adolescence clearly serves an adaptive function (Spear, 2013), it may also lead to various unhealthy outcomes (Nower, Derevensky, & Gupta, 2004).

In general, impatience can result from (a) the discounting of future outcomes, which may be a rather cognitive process and/or (b) increased sensitivity to immediate rewards, which may be more related to motivational forms of impulsivity (van den Bos et al., 2015). For instance, research suggests that the presence of an immediate reward makes people more impatient than when both options are in the future (McClure, Laibson, Loewenstein, & Cohen, 2004). However, previous developmental studies have not always been able to tease the different mechanisms apart.

Consistent with neurocognitive models of adolescent brain development, we recently reported age-related decreases in impatience between the ages 8 and 25, which was associated with increasing strength of the structural and functional connections between the dorsolateral

prefrontal cortex (DLPFC) and the striatum (van den Bos et al., 2015). Furthermore, a recent meta-analysis by Silverman and colleagues (2015) has shown that there is indeed evidence for heightened reward related activity in a wide network of regions, including the striatum. However, it is not yet well known how this heightened activity is related to increased impatient behavior. Recently, it has been suggested that the valuation network, in particular the striatum, not only matures earlier but that its functioning is modulated by pubertal hormones (Crone & Dahl, 2012). In line with such an idea, animal studies have demonstrated that testosterone significantly influences dopamine neural transmission in the adolescent brain, involving parts of the striatum as key targets (Allen, Purves-Tyson, Fung, & Shannon Weickert, 2015). In addition, Braams and colleagues (2015) have shown that pubertal testosterone is associated with an increased response to rewards in the striatum. Nevertheless, the specific pathways through which pubertal changes may affect different processes underlying impatient decision-making remain unknown (for a review see Laube & van den Bos, 2016).

Hypotheses

We hypothesized that pubertal testosterone would be specifically related to sensitivity to immediate rewards, whereas increasing age would be associated with a general decline in impatience.

Methods and Design

We tested $N = 72$ adolescent boys between the ages of 11 and 14 years. We assessed two morning salivary testosterone measures and a self-report questionnaire that measured external pubertal status, the pubertal developmental scale (PDS), in order to better differentiate between individual and developmental differences. Participants completed an intertemporal choice task with 80 trials in total. Here, they always had to choose between a smaller sooner

monetary reward and a larger later monetary option. Notably, in order to test sensitivity towards immediate rewards, for half of the trials the SS options were in the present, while the other half of the SS trials were in the near future. We performed beta regression and fitted a series of discounting models, including Bayesian model comparison techniques for comparison.

Major findings

Consistent with previous studies, we found that age, but not testosterone, is associated with an overall decline in discounting in early adolescence, and testosterone but not age is associated with increased sensitivity to immediate rewards.

Paper III

Laube, C., Lorenz, R. & van den Bos, W. (under review). Pubertal Testosterone Correlates with Adolescent Impatience and Dorsal Striatal Activity. *Nature Neuroscience.*

In this paper, we tested alternative hypotheses on how pubertal testosterone may affect impatient behavior in adolescence via distinct striatal pathways, particularly focusing on the distinction between the ventral and dorsal striatum. To get a precise description of these neural relationships and how they are related to task-related impatient behavior, we combined measures of fMRI, hormonal assessment and cognitive modeling to further disentangle processes related to value calculation (ventral striatum) and executive control (dorsal striatum) underlying decision making in puberty.

Theoretical background

Recent research emphasizes *puberty* as a key maturational process involved in risky and impulsive behaviors (Crone & Dahl, 2012; Forbes & Dahl, 2010; for a review see also Laube & van den Bos, 2016). Puberty defines the onset of adolescence and is characterized by a surge in pubertal hormones, including testosterone. These hormones are hypothesized to impact specific brain areas, which in turn may lead to changes in behavior promoting impulsivity and risk-taking (Blakemore et al., 2010; Crone & Dahl, 2012; Forbes & Dahl, 2010; Peper & Dahl, 2013). However, to date little is known about how pubertal testosterone is impacting the adolescent brain. Behavioral and self-report studies support the hypothesis that pubertal testosterone is related to *increases* in risky and impulsive behavior. Recent neuroscientific findings suggest two possible mechanisms that describe how increased testosterone may result in these behaviors.

First, pubertal testosterone may specifically impact computations in the *ventral* striatum, which is part of a valuation network that is mainly thought to code the subjective

value of rewards independent of domain (Bartra, McGuire, & Kable, 2013; Kable & Glimcher, 2007), and also preferentially for immediate rewards (McClure et al., 2004). Second, animal studies point towards the *dorsal* striatum as a key target of pubertal hormones (Matthews, Bondi, Torres, & Moghaddam, 2013; Sinclair, Purves-Tyson, Allen, & Weickert, 2014; for a review see Laube & van den Bos). Both the ventral and dorsal striatum receive projections of the dopamine system (Haber & Knutson, 2009), yet they differ based on distinct afferent projections (providing input) from cortical areas (Tziortzi et al., 2014). While the ventral striatum receives input from areas associated with reward processing, including limbic regions, the dorsal striatum receives its main afferent connections from the frontal cortex (Balleine, Delgado, & Hikosaka, 2007; Haber & Knutson, 2009; Tziortzi et al., 2014). In line with its connectivity profile, the dorsal striatum is associated with top-down modulation of learning and decision-making (Dayan & Berridge, 2014; Frank, 2011), and thus involved in executive control.

In sum, potential effects of testosterone on ventral and dorsal striatal regions are two distinct pathways of influencing decision-making processes in early adolescence.

Methods & Design

We investigated developmental differences in impatience of 75 boys aged between 10 and 15 years old, using an intertemporal choice task. The task, partly performed in a magnetic resonance imaging MRI scanner, was set up to specifically test for sensitivity to immediate rewards. To measure pubertal testosterone, we collected two independent morning saliva samples (Laube et al., 2017). The focus of the imaging analyses was based on ventral and dorsal striatal regions of interest (ROIs) that were selected based on their connectivity patterns (van den Bos et al., 2015; Tziortzi et al., 2014). Finally, we used computational modeling to gain further insight in the specific cognitive processes that underlie puberty related changes in impulsivity.

Hypotheses

We hypothesized that testosterone may impact the ventral striatum, which in turn would lead to its increased responsiveness for immediate over delayed rewards. On the other hand, for the dorsal striatum, we predict that testosterone would lead to decreased activation mirroring a reduction of the impact of prefrontal control areas. This decreased activation may directly lead to a shift towards more impatient behavior (Smith et al., 2016).

Major findings

We found support for the hypothesis that testosterone would lead to a reduction of dorsal striatal involvement (Matthews et al., 2013) and subsequently a reduced impact of prefrontal control areas, which biased behavior towards choosing smaller sooner rewards (Smith et al., 2017). However, we did not find evidence that testosterone enhanced ventral striatum valuation of immediate rewards (Braams et al., 2015).

Paper IV

Laube, C. & van den Bos, W. (unde review). It's About Time: How Integral Affect Increases Impatience. *Emotion.*

In this paper, we investigated whether integral affect leads to increased or decreased impatient behavior. We tested affect related changes in time perception as one critical mechanism that may explain a potential impact of affect in impatient choice. We conducted two studies with $N = 23$ and $N = 55$ participants, respectively, in which they had to complete an intertemporal choice task with relatively affect-rich and relatively affect-poor outcomes. In addition, they completed a future time judgment task.

Theoretical background

Affect is integral to most decisions in our everyday life. For instance, people may have difficulty saving for a flat because they keep spending money on enjoyable, but more immediate items and events (e.g., vacation). Research is sparse about how affect influences these types of intertemporal choices. Studies examining the impact of *incidental* affect (i.e., affect that is unrelated to a decision, such as a person's mood) suggest that positive affect leads to increased impatience (Kim & Zauberman, 2013; Van den Bergh, Dewitte, & Warlop, 2008; Wilson, Lengua, Tininenko, Taylor, & Trancik, 2009). Time perception represents the most prominent explanation for the effect of incidental affect on impatient behavior: Increased attention to time (Cappella, Gentile, & Juliano, 1977; Twenge, Catanese, & Baumeister, 2003) and/or heightened arousal (Droit-Volet & Meck, 2007) is hypothesized to make people overestimate the duration of time intervals. Consequently, as waiting time is considered a cost, the larger later reward appears less attractive, and people instead tend to prefer smaller but sooner options (Kim & Zauberman, 2013; Wittmann, Leland, Churan, & Paulus, 2007; Wittmann & Paulus, 2008). Additionally, studies on the role of *integral affect*

(i.e., affect that is caused by the decision itself) in risky choice suggest a stronger focus on outcomes (Pachur et al., 2014; Rottenstreich & Hsee, 2001; Suter, Pachur, & Hertwig, 2015), which would result in increased patience in the temporal domain. Alternatively, one could hypothesize that, in the context of intertemporal choice, affect results in more weight being put on the temporal attribute of the choice, thus leading to more impulsive behavior. In conclusion, we hypothesized that a future option associated with a significant amount of positive integral affect (e.g., meeting a favorite movie star in two months) increases arousal, which in turn leads to a changed time perception such that it makes the delayed option seem even further in the future and thus less attractive. Given that the delayed option is now even less attractive people make more impatient, sooner smaller, choices. Additionally, one could hypothesize that, in the context of intertemporal choice, affect results in more weight being put on the temporal attribute of the choice, thus leading to more impulsive behavior. To our knowledge, little is known about how integral affect impacts intertemporal preferences. The aim of this study was to test complementing hypotheses about the mechanisms underlying the impact of positive integral affect on intertemporal choice.

Hypotheses

We hypothesized that integral affect results in increased impatient behavior because it (1) leads to a distortion in time perception and/ or (2) leads to a shift in the weighting of choice attributes, so that individuals put more weight on the temporal (compared to the outcome) attribute.

Methods and Design

We conducted two studies, in which we used a within-subjects design and independently measured participants' impatient behavior and future time perception for affect-rich and affect-poor outcomes. In a first study with $N = 23$ participants, we assessed choice behavior

using an intertemporal choice task closely related to an experimental paradigm developed by Pachur and colleagues (2014) for the risk domain. We were thus able to systematically compare affect-rich and affect-poor choices—to our knowledge, for the first time in the field of impulsive choice. We then fitted participants' responses from the affect-rich and affect-poor condition to a series of common descriptive and heuristic intertemporal choice models in order to examine differences in the underlying mechanisms. To examine whether future time perception is prolonged in an affect-rich context, we systematically compared future time perception for affect-rich and affect-poor outcomes. In a second study, we hoped to replicated the findings in a larger sample with $N = 55$ participants and added an additional post-decision questionnaire to test if affect leads to a shift in the weighting of choice attributes (outcome versus delay).

Major findings

Across both studies, we consistently found that increased levels of positive affect were associated with an increase in impatient choices. That is, in affect-rich contexts, people more often chose the smaller but sooner reward. A shift in time judgment may explain this increased impulsive behavior: Our findings show that people judged future durations to be longer when considering options associated with high positive affect than when considering options with lower positive affect. Consequently, the future option's value seems less appealing, which in turn leads people to opt more often for the sooner but smaller reward. In addition, a shift in time judgment was also related to a shift in the weighting of the options' temporal attributes. That is, individuals who placed more emphasis on temporal information in the context of affect-rich choices also showed greater distortion in temporal judgment due to integral affect.

5. Discussion

5.1 Summary and Evaluation of Major Findings

Testosterone released in puberty may explain increased adolescent impatient choice in an affective context

In *Paper II*, I showed that testosterone was specifically associated with a sensitivity towards immediate options. Interestingly, neuroanatomical studies highlight the involvement of pubertal testosterone in reward related processing, such as its modulation of the striatal dopamine system in rodents (see also *Paper I*), but also in human adolescents (Braams et al., 2015). Consequently, one possible mechanism how testosterone is impacting sensitivity towards immediate options is via its enhancement of reward-related brain regions, such as the ventral striatum. While I specifically tested this hypothesis in *Paper III*, I did not find evidence for this hypothesis. Nevertheless, results in *Paper IV* illustrated a role for integral affect in intertemporal choice. That is, integral affect lead to increased choices for smaller sooner rewards, and hence more impatient behavior in *young adults*. Presumably, this so-called affect gap may be even larger for adolescents (see future directions for generation of specific hypotheses). This idea is also in line with research consistently showing higher impulsive choices for adolescents compared to other age groups when using highly affective stimuli (Figner, Mackinlay, Wilkening, & Weber, 2009; O'Brien et al., 2011). Particularly, a study by Somerville, Hare and Casey (2011) also showed that the presence of emotional stimuli was accompanied by an adolescent peak in the ventral striatum. Based on these findings, I propose that it will be more likely to find a relationship between testosterone and ventral striatal activity when using affective manipulations, which in turn may lead to an oversensitivity of immediate choices (based on *Paper II*).

The redefinition of the role of testosterone in adolescence: A novel framework

In *Paper III*, I specifically investigated the underlying neural mechanisms of developmental changes in impatient behavior across adolescence, resulting in the discovery of novel insights into the role of testosterone in puberty. Opposed to the long-standing hypothesis that pubertal hormones may impact reward related regions, such as the ventral striatum, and thus increase "reward sensitivity", I did not find support for that hypothesis. Conversely, motivated by findings from the animal literature reviewed in *Paper I*, I also tested if pubertal testosterone is related to the dorsal striatum, a region associated with cognitive control. Indeed, I found support for this hypothesis and was able to interpret findings based on concrete choice behavior, which allowed me to specify precise mechanisms by applying cognitive modeling techniques – an important feature that is missing in the majority of studies investigating adolescent brain development (van den Bos & Eppinger, 2015). Importantly, my results extend previous findings on the relationship between testosterone and striatal functioning in an important way by introducing a framework that highlights the functional differences of sub-regions within the striatum. Previously, instead of proposing a low (Forbes et al., 2010), or high (Braams et al., 2015; Op de Macks et al., 2011) "reward reactivity", I suggest an additional role of testosterone distinct from reward sensitivity and rather implicated in modulating the impact of frontal control.

Specifically, the dorsal striatum has often been implicated in action-contingent learning (Balleine et al., 2007; O'Doherty, 2004) and testosterone may impair this type of learning, which would have several implications on previous findings relating testosterone and risk taking (Op de Macks et al., 2016; Op de Macks et al., 2011; Peper, Koolschijn & Crone, 2013). That is, several of these studies have used the Balloon Analog Risk Task (BART; Lejuez et al., 2002) to measure risk taking (e.g. Aklin, Lejuez, Zvolensky, Kahler, &

Gwadz, 2005; MacPherson, Magidson, Reynolds, Kahler, & Lejuez, 2010; Romer et al., 2009; Telzer, Fuligni, Lieberman, & Galván, 2013). Importantly, one of the essential features of the BART is that it is a learning task. Using this task, Peper and colleagues (2013) concluded that higher levels of testosterone were associated with higher levels of risk taking mediated by smaller medial orbitofrontal cortex gray matter volume, a region that is strongly connected to the dorsal striatum. Based on my findings it could be hypothesized that it is specifically the role of testosterone in action outcome learning that is leading to differences in risk taking, instead of modulating risk preferences directly. Studies separating risk from learning aspects would deliver fruitful insights into this proposed hypothesis.

Implications on early puberty

The age of pubertal onset has lowered significantly in recent decades, which is associated with increased risk of psychiatric diseases (Whittle et al., 2012) and lower educational achievement (Copeland et al., 2010). Using a multiple-process perspective, as illustrated in both *Paper II* and *III*, generates interesting and testable predictions of how the timing of pubertal onset shapes impatient behavior during adolescence, which in turn has been shown to correlate with academic achievement (Duckworth & Seligman, 2012), substance abuse, conduct disorder, and a range of developmental disorders including attention deficit hyperactivity disorder (ADHD). For instance, Martin and colleagues (2001) found that retrospective report of early pubertal onset was associated with increased sensation seeking and substance use in both males and females, while controlling for gender differences in onset. Thus, *early* entrance into puberty may amplify the effects of testosterone on impatience, whereas *late* entrance may dampen its effects because frontal regions are, by this time, more developed (Gogtay et al., 2004; Tamnes et al., 2017; see Khundrakpam, Lewis, Zhao, Chouinard-Decorte, & Evans, 2016).

My findings in *Paper III* enable an even more precise description, based on our suggestion that impatient behavior in adolescence seems to be due to an imbalance between increases in executive control, due to increasing structural connectivity between the dorsal striatum and prefrontal cortex on the one hand (Achterberg, Peper, van Duijvenvoorde, Mandl, & Crone, 2016; van den Bos et al., 2015),and reductions due to testosterone's modulation of presumably the same corticostriatal circuit on the other hand. Based on my results, I hypothesize that an early entry into puberty may amplify the effects of testosterone by specifically leading to stronger reduction of prefrontal control, given that it is less developed compared to a later entry into puberty. In addition, recent research suggests that pubertal hormones may regulate plasticity in the prefrontal cortex and thus learning (Juraska & Willing, 2017; Piekarski et al., 2017), which also emphasizes that the timing of educational and psychiatric interventions may be dependent on pubertal onset in order to be successful.

5.2 Limitations of the Studies Reported

The need for longitudinal study designs

Within cross-sectional designs such as the ones used in the present dissertation, it is difficult to distinguish pubertal maturation from non-developmental individual differences in testosterone levels. Although the relationship between PDS and testosterone reported in both *Paper II* and *III* lends support to my interpretations, additional longitudinal investigations are needed to disentangle individual and developmental differences. Yet, two recent studies investigating the effects of testosterone on delay discounting in adult males showed no significant relationship (Ortner et al., 2013; Takahashi, Sakaguchi, Oki, & Hasegawa, 2008), suggesting that the function of testosterone in puberty may be distinct from its function later in life.

Nevertheless, in order to systematically test this idea, one would need to adapt a lifespan perspective. An interesting research goal for future studies would be to examine testosterone's function across the lifespan, and specifically test if testosterone serves a unique function in puberty, or if its effects may be rather attributed to a continuum, where the influences of testosterone during puberty are simply amplified due to large increases in circulating levels. In addition, studying the effects for estrogen, arguably the comparable gonadal hormone in females, from a lifespan perspective may be of particular interest given that during menopause, there is a rapid decrease in estrogen levels, possibly reflecting a second "pubertal phase". Finally, it is important to note that besides developmental differences, individual differences within a developmental period should be also of great interest, especially when seeking to identify possible risk groups, for example for psychiatric disorders, as these can be better understood when examining the full range of behavior from normal to abnormal.

Gender differences

An obvious limitation of the current dissertation is that all the insights regarding how testosterone released in puberty impacts impatience and the brain is limited to male participants. Thus, to this end, it remains unclear if pubertal testosterone has similar effects in adolescent girls compared to boys. There exist, to my knowledge, only two studies that examined the effects of testosterone on striatal function in girls (Forbes et al., 2010; Op de Macks et al., 2016). Out of these two studies, only Op de Macks and colleagues (2016) included task-related behavior and found a positive correlation between levels of testosterone and risk-taking, which was mediated by medial orbitofrontal cortex activation, an area showing major projections to the dorsal striatum (Haber & Knutson, 2009). Nevertheless, while pubertal development and testosterone are highly correlated in boys, there is no clear

association evident in girls (Granger, Shirtcliff, Booth, Kivlighan, & Schwartz, 2004; Maskarinec et al., 2005). Even Op de Macks and colleagues (2016) themselves suggest that testosterone in boys is thought to better capture developmental differences, while the effects of testosterone on girls may be more reflective of individual differences. In addition, gonadal hormones have been associated with differences in the rate of brain maturation during adolescence, showing that frontal sub-regions are those where cortical thickness in males is last to approximate that in females (Raznahan et al., 2010). Notably, impulsivity, the main construct investigated in the current thesis, varies considerably between genders. A meta-analysis by Cross, Copping and Campbell (2011) with N=277 studies and a total of N=149.496 participants reported significant sex differences for motivational forms of impulsive behavior, such as sensation seeking. In line with those findings, several large-scale developmental studies reported higher sensation seeking in boys compared to girls (D'Acremont & Van Der Linden, 2005; Steinberg et al., 2008).

Nevertheless, future studies should repeat the studies of *Papers II* and *III* in a group of girls. Interestingly, research on the effects of estradiol in women demonstrated its involvement in frontal dependent cognitive processing (Jacobs & D'Esposito, 2011; Joseph, Swearingen, Corbly, Curry, & Kelly, 2012). Similarly, evidence from the animal literature reported increases in dopamine signaling in the prefrontal cortex induced by estradiol, the predominant type of estrogen for females between menarche and menopause (Shansky et al., 2004). A recent study by Smith and colleagues (2014) found that a present bias (preferring immediate over delayed rewards) was negatively correlated with estradiol during the ovarian cycle. This literature clearly shows interesting parallels to my interpretations in *Paper III*. Thus, for future studies, I would be particularly interested to repeat the testosterone imaging study within a group of girls, both measuring their testosterone and estradiol levels across their menstrual cycle.

5.3 Future Research Directions

Adolescence as a sensitive period

A growing body of research highlights the importance of adolescence as a sensitive period of brain development (Fuhrmann, Knoll, & Blakemore, 2015). Gonadal hormones released in puberty impact grey matter volume globally (Peper, Brouwer, et al., 2009; Peper, Schnack, et al., 2009), as well as specifically, in regions such as in the hippocampus (Neufang et al., 2009), a key area in memory and learning. I think it will be a fascinating and promising project to combine the research areas of pubertal development and plasticity in the brain to precisely investigate and describe a potential "window of opportunity" for learning. In particular, to my knowledge, no study so far has investigated possible interactions between the timing of pubertal events and structural and functional brain development associated with learning.

Predictions for the affect gap in adolescence

In *Paper IV,* I found that integral affect increased impatience via changes in time perception. Specifically, in an affect-rich context, future time seemed to be prolonged, which presumably made the larger later reward less attractive. In addition, individuals also put more weight on the temporal attribute when deciding between affect-rich compared to affect-poor rewards. Yet, this study was performed in two independent groups of *young adults*. Since the focus of the current dissertation is adolescence, the next crucial question that has to be answered in future studies is the following: Is there such as an affect gap in adolescence, and if so, are the mechanisms the same as those in early adulthood, in other words, can time perception explain

potential developmental differences in the affect gap? As thoroughly summarized in *Paper I* and also throughout the current dissertation, there is plenty of reason to believe that affect during adolescence is driving impatient decision-making. Thus, I hypothesize that the extent of the difference in smaller sooner choices between an affect-rich and affect-poor domain is larger in adolescents compared to adults. Regarding predictions for time perception, my results in *Paper III* may help to speculate about potential hypotheses, as they have highlighted the corticostriatal network, specifically the dorsal striatum in its involvement in impatient behavior during puberty. For instance, a review by Meck, Penney and Pouthas (2008) highlighted the same network being involved in time perception in adults. In addition, Rammsayer (1997) reported that reductions in dopamine lead to impairments on processing of longer durations. Similarly, I summarized in *Paper I* that pubertal testosterone is also associated with reduced dopamine levels in the rodent dorsal striatum, which in turn has shown to lead to a present bias in human adults (Smith et al., 2016). This finding is consistent with evidence linking deficiencies in dopamine signaling with an overestimation of time (see Merchant, Harrington, & Meck, 2013). Together, I hypothesize that adolescents show increased overestimation of time compared to adults, which may explain potential developmental differences in the affect gap in intertemporal choice.

What about pubertal tempo?

Although pubertal onset is occurring at lower ages, earlier offset of puberty as indexed by final height or menarche, has not been reported (Mendle, 2014). It is hypothesized that earlier pubertal timing is associated with slower pubertal tempo (Lee & Styne, 2013). Pubertal tempo is defined as the time it takes an individual to progress through the different stages of puberty. That is, the longer individuals take to reach the next stage in their pubertal development, the

slower their pubertal tempo. Changes in the relationship between pubertal timing and pubertal tempo may reflect a compensatory response.

Adolescents show large variations in the duration of puberty (Marceau et al., 2012; Marshall & Tanner, 1970), but little is known about why some individuals progress faster through puberty than others (Mendle, 2014). To date, the majority of studies that investigate risky and impulsive behavior in adolescence, including those in the current dissertation, only include measures of pubertal status. However, research on both pubertal timing and tempo points towards its involvement in adolescent health and academic success. For instance, studies on adolescents' psychopathological symptoms showed that early pubertal timing has been identified as disruptive for both boys (for a review see Mendle & Ferrero, 2012) and girls (for a review see Mendle, Turkheimer, & Emery, 2007). In addition, pubertal tempo has been shown to relate to daily affective experience. Specifically, affect was more negative and more variable when pubertal changes occurred faster (Hunt, 1999; Mendle, Harden, Brooks-Gunn, & Graber, 2010).

Taken together, adolescents differ remarkably in at least three aspects of pubertal development: status, timing, and tempo, resulting in large heterogeneity within adolescent populations. Thus, combining measures of pubertal status, timing, and tempo will prove to be particularly useful when seeking to understand the full range of pubertal changes and how these may be related to changes in risky and impulsive decision making in adolescence.

Dual Hormone Hypothesis

In *Paper II,* I showed that pubertal testosterone and age have independent effects on impatient behavior in adolescent boys. Specifically, results suggest that increased testosterone, but not age, is related to increased sensitivity to immediate rewards, whereas increased age, but not testosterone, is related to a reduction in general impatience.

Nevertheless, a relatively novel theory, the dual-hormone hypothesis, proposes that the impact of testosterone on behavior should only depend on concentrations of cortisol (Mehta & Josephs, 2010). In detail, the theory predicts that testosterone should be positively correlated with behavior only when cortisol concentrations are low. In contrast, when cortisol concentrations are high, the effects of testosterone on behavior should be inhibited or blocked. Mehta and Prasad (2015) reviewed empirical evidence on the dual-hormone model and found a testosterone by cortisol interaction in multiple domains of human social behavior, such as dominant leadership behavior (Mehta et al., 2010); social status (Edwards & Casto, 2013); aggressive and violent behavior (Dabbs, Jurkovic, & Frady, 1991; Popma et al., 2007); antisocial economic punishment in a public goods game (Pfattheicher, Landhäußer, & Keller, 2013); empathy (Zilioli, Ponzi, Henry, & Maestripieri, 2015); overbidding in auctions (Van Den Bos, Golka, Effelsberg, & McClure, 2013); and risk-taking (Mehta, Welker, Zilioli, & Carre, 2015). However, several open questions remain: (1) What are the underlying mechanisms explaining the dual-hormone hypothesis? Furthermore, and most important for our research field, (2) is a testosterone by cortisol interaction also apparent in adolescents and if so, (3) are the behavioral consequences of that interaction the same as predicted by the dual-hormone model?

Interestingly, studies have shown that basal cortisol levels increase with both age and pubertal development (Gunnar, Talge, & Herrera, 2009; Kiess et al., 1995; Matchock, Dorn, & Susman, 2007; Netherton, Goodyer, Tamplin, & Herbert, 2004; Sinclair et al., 2014), whereas testosterone is rather thought to increase only with the latter. Thus, the distinct effects of age and pubertal testosterone on impatience may be explained by different levels of cortisol. Given that research on the dual-hormone hypothesis is still in its infancy, we could meaningfully contribute to the field by integrating a measure of cortisol in future studies. Including measures of cortisol would also help us to better understand the role of pubertal testosterone in adolescent impatient behavior, for instance by being able to formulate more

precise predictions and to better understand the function of testosterone within this developmental group.

5.4 Conclusions and Outlook

The aim of the present dissertation was to advance the understanding of neural, endocrinological and contextual mechanisms underlying impulsive decision-making in adolescence. Throughout my work, it becomes clear that integrating measures of pubertal development is vital when trying to resolve the mysteries and inconsistencies of teenage behavior and brain development. Furthermore, when specifically breaking down broad psychological constructs such as impulsivity into specific and quantifiable processes, distinct developmental variables such as pubertal testosterone and age show differential effects on developmental trajectories. The most striking and important finding of the current dissertation is the relationship between pubertal testosterone and dorsal striatal activity. In contrast to previous theories rooted in the traditional dual-systems approach, suggesting that pubertal hormones impact the subcortical reward system and thus leads to its "hyperactivation", we do not find support for this. Instead, our results rather point towards an association between pubertal testosterone and cognitive control, which, provided future studies can replicate our findings, would lead to a redefinition of current models of adolescent brain development.

As a final note, I also would like to highlight that contrary to the oft-described pathological view of adolescence in our culture, the physiological and behavioral changes occurring during adolescence clearly serve an adaptive function. Against the background that puberty is a distinct developmental stage, showing striking similarities between species and cultures in puberty related changes of brain physiology and behavioral patterns, being impulsive may also be adaptive as it is deeply rooted in evolutionary history. For instance, as the peer group receives increased meaning during adolescence, identity formation highly

depends upon the opinion of friends. This also results in increased uncertainty about the stability of preferences, which may cast impulsivity in a new light. Put differently, choosing to do or to get something today rather than in the future may be adaptive for adolescents, simply because of high uncertainty in your own future preferences.

Future research should seek to highlight the adaptive elements of adolescence behavior, as increased impulsivity in specific contexts may be beneficial in later stages in life. While there is still a lot to learn for teenagers, we as the adults can clearly also learn a lot from the adventurous and explorative attitude of adolescents.

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