Decision and Reward in Intertemporal Choice: The Roles of Brain Development, Inter-individual Differences and Pharmacological Influences

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The following parts of this thesis have already been published in or will be submitted to international peer reviewed journals:

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Abstract

Human decision making is closely related to reward processing because many decisions rely to a certain degree on the evaluation of different outcome values. Reward-based decisions can be health-related, for example if someone has to compare the outcome value of the instant reward of smoking a cigarette to that of the long term goal of keeping well and fit. Such comparisons do not only rely on the nominal value of the alternatives but also on devaluation of rewards over time. The value of being healthy at older age might outweigh the value of smoking a cigarette but since the payoff of the health-outcome will be delayed, humans tend to decrease the value of this option. Therefore in this example one might choose the immediate reward of smoking a cigarette. The proclivity to devaluate the value of rewards over time has been widely investigated with experimental intertemporal choice tasks, in which subjects have to choose between smaller sooner rewards and larger later rewards. A stronger individual devaluation proclivity (i.e. discounting rate) has been reported to be related to addiction. Research in neuroeconomics has suggested the competing neurobehavioural decision systems (CNDS) theory, proposing that an imbalance between an executive (cortical prefrontal brain areas) and an impulsive (i.e. subcortical areas, such as ventral striatum (VS), amygdala) system in the brain leads to steeper discounting and a higher risk for addiction. Additionally, temporal discounting has been proposed as a trans-disease process, i.e., "a process that occurs across a range of disorders, making findings from one disorder relevant to other disorders" (Bickel, Jarmolowicz, Mueller, Koffarnus, & Gatchalian, 2012, Abstract). Thus, the CNDS theory and temporal discounting might also have implications for other health-related behaviour than substance use.

So far many factors have been shown to be associated with higher discount rates: for instance, adolescent age, lower intelligence and nicotine dependence. Further, it has been

shown that adolescents are at highest risk to start smoking. On the other hand a higher education level has been shown to be associated to lower rates of smoking. Thus, it seems likely that a higher discount rate might be one reason why adolescents experiment with smoking, why lower education is associated to nicotine addiction and why dependent smokers are not successful in smoking cessation. But relatively little is known about the neural processes behind these variables, which could be also seen as exemplary risk- and protective factors regarding addiction. The 3 studies of the thesis at hand were conducted to extend the knowledge about neural processes associated to age, intelligence and smoking in their relation to intertemporal choice. The task was chosen because of its relevance for addiction and a variety of health-related behaviour.

The first study was conducted to explore the neural correlates of age related differences between adolescents at age 14 and young adults during intertemporal choices. Additionally, the roles of discounting and choice consistency were investigated. Although adolescents discounted delayed rewards more steeply than adults, neural processing of reward value did not differ between groups, when controlling reward values for the individual discount rates. However, a higher discount rate was related to a lower responsivity in the ventral striatum to delayed rewards, independent of age. Concerning decision making, adolescents exhibited a lower consistency of choices and less brain activity in a parietal network than adults (i.e. posterior and inferior parietal regions). Thus, reward value processing might be more sensitive to the discount rate than to chronological age. Lower consistency of intertemporal choices might indicate ongoing maturation of parietal brain areas from adolescence to young adulthood.

The second study was conducted to reveal the associations between neural processes of decision making and intelligence in adolescents. The results of *study 2* revealed networks in the adolescent brain where brain activity was related to crystallised intelligence as well as

to intertemporal choice behaviour. Specifically, during decision processing higher crystallised intelligence as well as more consistent decisions were associated with higher brain activity in the posterior parietal cortex. Processing of delayed rewards was also related to crystallised intelligence, i.e. more intelligent adolescents showed higher brain activation in the anterior cingulate cortex (ACC) and the inferior frontal gyrus (IFG), which was in turn related to a lower discount rate. Additionally, associations between the parental education level and crystallised intelligence of the adolescent participants of the study and their discount rate were found, indicating that parental education as an environmental factor could be related to a lower risk for addiction. This protective effect might be mediated by the offspring's crystallised intelligence and discount rate which are both related to brain activity in parts of the same brain networks (i.e. the IFG).

The third study was done to investigate neural processes of intertemporal decisions in smokers and non-smokers. To test whether the effects of smoking on the discount rate are due to chronic or acute nicotine intake, non-smokers were additionally assessed under acute nicotine administration. *Study 3* revealed that the effects of nicotine on intertemporal choice behaviour were related to chronic intake of nicotine in smokers rather than to acute nicotine administration in non-smokers. Regarding the neural processes, smokers compared to non-smokers showed lower brain activity in the posterior parietal cortex. Comparable but weaker effects were found under acute nicotine in non-smokers. Although acute nicotine administration altered neural processes, behavioural changes might only occur after repeated nicotine intake. However, the study did not preclude that the differences are pre-drug characteristics.

Altogether the studies revealed overlapping neural correlates of intertemporal choices which are related to the individual age, the discount rate, the choice consistency, the individual intelligence as well as acute and chronic nicotine intake. This might provide an integrative view on how inter-individual differences and behaviour during intertemporal choices are

based on common neural correlates which in turn might have implications for the development and the maintenance of addiction. Specifically, hyposensitivity towards delayed rewards in the adolescent ventral striatum, which has also been found in smokers compared to non-smokers, is associated with higher discount rates and higher risk for smoking initiation. In contrast, higher activation in the IFG and the ACC in more intelligent individuals during reward value processing might enhance behavioural inhibition and control and, hence, might prevent nicotine addiction. In line with the CNDS theory responsivity in subcortical brain areas (i.e. impulsive system), such as the VS was related to the risk factor of adolescent age, whereas activity in cortical areas (IFG and ACC) was related to the protective factors of higher crystallised intelligence.

Since there was only one study beside the studies of the current thesis reporting results regarding consistency, one can only speculate about implications for health-related behaviour, such as addiction. Consistency might play a role, especially for cessation success. Thus, the findings that adolescents as well as less intelligent individuals were less consistent might point to a higher risk for maintenance of nicotine addiction. The higher brain activity in a fronto-parietal network, which has been shown in *studies 1 and 2* in adults as well as in more intelligent adolescents, was related to higher consistency of choices in both studies. Thus, the finding might be a possible neural correlate for the association between the risk factor of adolescent age, the protective factor of higher crystallised intelligence, and more consistent decision making.

In conclusion the findings of the current thesis contribute to a better understanding of how inter-individual differences and environmental factors might be accompanied by neural processes which in turn might be related to individual development of addiction. Further the results might extend the CNDS theory regarding neural correlates of exemplary risk and protective factors regarding adolescents' health behaviour and smoking in adults.

1 General Introduction

1.1 Decision making and rewards in relation to intertemporal choice and health-related behaviour

The ability of human beings to make decisions is of great importance for plenty situations in life, e.g. decisions affecting health and well-being or economic issues. All these decisions, regardless of the context, are based on expected value and certainty of the outcome and depend on individual differences. Decision outcomes can either be positive, such as the rewarding effect of smoking a cigarette for the smoker or negative, such as losing money at the stock exchange. In the case of the choice between two rewards the decision depends on the reward value of different options and how these values are weighted. Thus, in this case decision making is closely related to reward processing.

Intertemporal choice tasks (also referred to as temporal discounting or delay discounting tasks by different authors) provide an experimental approach that merges decisions and rewards. The task tests and describes the preference to choose a larger reward in the future compared to a smaller one obtained earlier (Ainslie, 1975). Because of its high relevance for reward decision making, it has been widely investigated in economics (for a review see Ho et al., 2006) as well as in psychology (see review of Loewenstein et al., 2008). In each trial of an intertemporal choice task individuals have to decide whether they want a small reward paid earlier or a larger one paid later (e.g. 10 Euro now or 20 Euro in 30 days). Usually, subjects choose the reward whose reward value outweighs the other one. In the case of intertemporal choices the value of a monetary reward depends on the individual proclivity to discount rewards over time as well as on the delay and the amount of the payoff.

Generally, the task reflects the decision between a short term outcome and long term goal attainment. An example for an economic decision is the individual decision whether one wants to buy a sportscar right now or to invest the money in a retirement arrangement plan. The retirement arrangement plan would be more valuable than the sportscar at the time of payoff. But since this is at a time far away in the future and future rewards usually are affected by devaluation (i.e. discounting), the individual might decide for the sportscar. This decision might not be rational in a strict economic sense.

Decisions relying on discounting of later rewards can also be health-related. For example the decision between the instant reward of smoking a cigarette or keeping well and fit at older age. Most of the studies, providing results regarding discounting and its association to health-related behaviour, has been conducted in addiction research, e.g. alcohol dependence (e.g. Bjork, Hommer, Grant, & Danube, 2004a), gambling (e.g. Holt, Green, & Myerson, 2003) and nicotine dependence (e.g. Bickel, Odum, & Madden, 1999). However, several studies have shown associations between other health-related behaviour and temporal discounting. Specifically, discounting has been shown to be related to behaviour, such as disease screening, physical activity, nutrition, managing stress, avoiding destructive habits, practicing safe sex, adopting safety habits, knowing first aid, personal health habits, using medical advice (Bradford, 2010; Melanko & Larkin, 2013), the Body-Mass-Index (Zhang & Rashad, 2008), obesity in women and adolescent smokers (Davis, Patte, Curtis, & Reid, 2010; Fields, Sabet, Peal, & Reynolds, 2011; Weller, Cook, Avsar, & Cox, 2008) and risky sexual behaviour in adolescents and young adults (Chesson et al., 2006). All these studies found a negative association between discounting and health-related behaviour, because in most cases when deciding between two options, the healthier option requires long-term orientation. Thus, recently temporal discounting has been proposed as a trans-disease process, which is a common process underlying not only addictions but also other diseases. Consequently, results of studies

regarding intertemporal decisions might not only be relevant for the study of addiction but also for health-related behaviour in general (cf. Bickel et al., 2012).

In addition to the amounts of behavioural results, there are many studies which have investigated neural processes underlying intertemporal decision making. Neuro-imaging studies showed that the decision making process is related to brain activity in a fronto-parietal network (Hoffman et al., 2008; McClure, Laibson, Loewenstein, & Cohen, 2004), whereas the reward value is processed in the reward circuitry including the ventral striatum and the medial prefrontal cortex (Kable & Glimcher, 2007; Peters & Buchel, 2009; 2010). There has been a debate on how the brain processes intertemporal choices. Whereas McClure et al. (2004) proposed two systems, an impulsive β-system which is involved in decisions when one immediate option is available and a δ-system which is related to all decisions. The β-system refers to the same brain areas Kable & Glimcher (2007) also referred to in a later study and which were found to be related to the subjective value of delayed rewards. Meanwhile several studies have shown that these regions seem to process subjective value rather than choices with an immediate option (eg. Peters & Buchel, 2009; 2010; study 1, 2 and 3 of the current thesis).

Neural underpinnings of health-related behaviour have been first proposed in the field of addiction which is a very well investigated health-related behaviour. It has been proposed that an imbalance of two competing systems of the brain (i.e. 1. executive 2. impulsive) causes suboptimal decision making regarding intertemporal choices and is hence associated to addiction (Bechara, 2005; Bickel et al., 2007). Recently, this hypothesis has been extended to other health-related behaviour and was referred to as competing neurobehavioural decision systems theory (CNDS, Bickel et al., 2012).

The question how an individual decides during intertemporal choices relies on individual characteristics, e.g. age (Green, Myerson, & Ostaszewski, 1999), personality or cognitive ability (Shamosh & Gray, 2008). Regarding health-related behaviour studies have shown

that adolescents are at high risk to initiate substance use (Palmer et al., 2009), that higher rates of discounting delayed rewards might be a risk factor for substance use disorders (MacKillop et al., 2011). In contrast, a higher education level is associated with lower rates of smoking (Jefferis, Graham, Manor, & Power, 2003). Thus, adolescent age might be a risk factor, whereas higher education might be a protective factor. Both will be used in the current thesis to show exemplarily how such factors may be associated to neural processes of intertemporal choices, which are in turn of relevance for health-related behaviour. Until today, there are relatively few results about the neural processes behind risk and protective factors regarding health-related behaviour in general.

The current thesis aimed at showing possible neural correlates of exemplary risk and protective factors in reward decision making, which is closely related to health-related behaviour. For that purpose neural processes of intertemporal decision making were investigated in all studies of the thesis at hand. The first study was done to find the neural correlates of age related differences between adolescents and young adults, because adolescence is a period of increased risky behaviour, including health-related behaviour, such as substance use (Arnett, 1999; Crone & Dahl, 2012). Furthermore, foundations for psychiatric illness might be established during this life period (Sawyer et al., 2012). The second study was done to reveal the associations between neural processes of decision making and intelligence in adolescents, since higher educational achievement has been shown to be preventive against becoming a persistent smokers later in life (Jefferis et al., 2003). The third study was done to investigate differences in neural processes of intertemporal decisions between smokers and non-smokers. To test whether the effect of smoking on the individual discount rate was due to chronic or acute nicotine intake, non-smokers were additionally assessed under acute nicotine administration. Altogether, by revealing neural processes behind the exemplary risk- and protective

factors the thesis might contribute to the understanding of risk- and protective factors regarding health-related behaviour and might extend the CNDS theory regarding these factors.

1.2 Individual chracteristics as behavioural measures of intertemporal choices

The individual discount rate and the consistency of choices are behavioural measures of intertemporal choices. These measures are individual characteristics which are related to age, personality traits, intelligence and substance use behaviour. Chapter 1.2.1 will introduce the discount rate as a measure of impulsivity and chapter 1.2.2 will introduce the choice consistency as a second behavioural measure of intertemporal choices. Further the relevance of the behavioural measures for mental health and daily life will be discussed.

1.2.1 The discount rate as a measure of impulsivity

Impulsivity is a broadly discussed and well investigated personality trait. This trait has several facets and can be measured via questionnaires as well as via behavioural measures. In general, an impulsive personality can be characterized by narrow impulsiveness, lack of planning, risk-taking and liveliness (Eysenck & Eysenck, 1977).

Several of the common personality questionnaires include an impulsivity subscale. Questionnaires measuring impulsivity in one of their subscales are the NEO five factor inventory (NEO-FFI, Mccrae & Costa, 2004), the temperament and character inventory (TCI, Cloninger, Svrakic, & Przybeck, 1993), or the substance use risk profile scale (SURPS, Woicik, Stewart, Pihl, & Conrod, 2009). There are also questionnaires which directly measure different facets of impulsivity (i.e. attentional -, motor - and nonplanning impulsivity), for example the Barratt impulsiveness scale (BIS, Patton, Stanford, & Barratt, 1995).

Beside the aforementioned questionnaires, behavioural measures also represent different aspects of impulsive behaviour. One facet which can be measured is the ability to stop

already planned motor behaviour (i.e. impulsive disinhibition) measured for example with the stop signal task (Logan, Schachar, & Tannock, 1997). Another facet of impulsivity is the ability to wait (i.e. impulsive decision making) that can be measured with an intertemporal choice task. These different measures represent different facets of impulsivity that are not necessarily correlated (Reynolds, Ortengren, Richards, & de Wit, 2006).

The facet of impulsivity used in the studies of the current thesis was impulsive decision making measured with an intertemporal choice task. This facet of impulsivity describes the individual discount rate of delayed rewards. The subjective discount rate can be shown as a curve, which is best described by a hyperbolic function (Mazur, 1987; Kirby & Herrnstein, 1995; Kirby & Marakovic, 1995; Kirby, 1997) using the following formula:

$$V = \frac{A}{1 + k \times D}.$$

In this formula V represents the subjective value of a reward, A represents the amount of a reward, D is the delay until the reward will be paid and k is the subjective discounting parameter which individually describes the discount rate of each individual.

As outlined in chapter 1.1 intertemporal decision making is relevant for health-related behaviour, such as substance use, physical activity or obesity. The decision between smoking a cigarette right now as an immediate reward or keeping well and fit in the future as a delayed reward is one example for an intertemporal choice, which might be related to nicotine addiction. The association between discounting of monetary rewards and smoking has been shown in several studies, for example by Bickel *et al.* (1999; for more details see chapter 1.5). Not only has temporal discounting been proposed to be a trans-disease process (Bickel et al., 2012), which might be associated to health-related behaviour, but also other facets of impulsivity have been associated with several psychiatric disorders, characterised by impulsive be-

haviour, such as personality disorders, bipolar disorder, attention deficit hyperactivity disorder (ADHD) and substance use disorders (for an overview see Möller et al., 2001).

The link between impulsivity and reward processing has been shown in several neuroimaging studies which investigated reward processing in the human brain. These studies have shown that impulsivity is associated to processing of rewards in alcoholics (Beck et al., 2009), psychopaths (Buckholtz *et al.* (2010) and Bjork *et al.* (2012)), adolescents with ADHD (Scheres, Milham, Knutson, & Castellanos, 2007) and healthy adults (Hariri et al., 2006). Although the results of these studies where not consistent regarding the direction of the effect, all studies interpreted the altered brain activity as a possible reason for differences in impulsivity. Moreover, steeper discounting has been shown to be higher in younger individuals (Green, Fry, & Myerson, 1994; Green et al., 1999), in less intelligent individuals (Shamosh & Gray, 2008) and in smokers (Bickel et al., 1999).

Because impulsivity is related to differences in reward processing in the brain as well as to possible risk and protective factors for health-related behaviour, it might be fruitful to consider impulsivity as a possible link between brain activity and risk and protective factors, such as age and intelligence.

1.2.2 Choice consistency as a behavioural measure of intertemporal choice

Reward related decisions during intertemporal choices do not only rely on value differences between the alternative rewards. Several factors such as adaptation to a certain situation or emotions might cause deviation from strict value-based decisions. Consequently, decisions are not absolutely consistent over time and situations. Since adapting to situations and balancing between exploration and exploitation is important, consistency is neither advantageous nor disadvantageous per se. The consistency of choices should be considered as a further behavioural measure of intertemporal choices referring to the degree to which subjects choose the alternative with the higher subjective value over the time course of the task. Thus,

consistency is related to the comparison of the two options during the decision making process. To decide consistently over all trials of an intertemporal choice task, each decision has to rely on the same evaluation (discounting rate), but also attention and decision difficulty might play a role.

A consistency parameter for decisions in general has been introduced for example in a formula (i.e. the softmax activation function) by Suton & Barto (1998). Although the evaluation of the delayed reward depends on the individual discount rate, consistency is conceptually and formally independent of the discount rate, i.e. steeper discounting can be related to high or low consistency. Consequently, the consistency measure contains additional information about the way decisions are made.

The only study reporting results regarding consistency revealed lower brain activity in the left inferior frontal gyrus (IFG) to be related to more consistent decision making in an intertemporal choice task. The lower BOLD was interpreted as reduced executive function demands in highly consistent participants (Luo, Ainslie, Pollini, Giragosian, & Monterosso, 2012). Beside this study, research has neglected the consistency of choices, even though the softmax activation function has been used by several studies investigating intertemporal decision making (e.g. Peters, Miedl, & Buchel, 2012; Pine, Shiner, Seymour, & Dolan, 2010).

The role of consistency has been briefly proposed by Luo *et al.* (2012) as being supportive in situations in which success needs consistent farsightedness, such as smoking cessation. For example consistency would contain the information whether an individual would choose the instant reward of smoking a cigarette or the long-term outcome of health in each situation (e.g. at home or when going out with friends who smoke). The question whether consistency is advantageous or not cannot easily be answered. For instance, higher consistency might be disadvantageous for a smoker but advantageous for a non-smoker. On the other hand, occasional smokers might be less consistent regarding smoking. The role of consistency

during the process of smoking cessation might also be more complicated than proposed by Luo *et al.* (2012). On the one hand, it might be harder for the highly consistent smoker to change behaviour. On the other hand, after a smoker has quit smoking and has to reject smoking cigarettes each time he has the opportunity to consume a cigarette, cessation success might benefit from higher consistency. Especially after a nicotine addiction treatment when smokers have learned to evaluate the reward value of the behavioural options (i.e. smoking or not) in a more long-term oriented way than before, the learned behaviour should be consistent not only in the setting of the treatment to prevent relapse. However, one can only speculate about the role of consistency regarding health-related behaviour and further research is needed to clarify its role in addiction.

As mentioned before, only one study (Luo et al., 2012) addressed the measure of consistency during intertemporal choices. Until today, no study tested age-, and intelligence-related differences in consistency. Therefore, the question whether consistency might be an additional link between risk and protective factors and brain activity is still open.

1.3 Neural reward processing and risk taking in adolescents and adults

Adolescence is the period in life, in which many novel experiences are made, e.g. romantic relationships, making decisions for the future independently of the parents or testing substances, like alcohol, nicotine or other drugs (Arnett, 1999; Steinberg, 2010). The latter example shows the relevance of health-related behaviour. Howsoever, all of these novel experiences are presumed to be related to structural as well as to functional changes in the adolescent brain, because structural brain development, especially in the frontal lobe of the brain, lasts until young adulthood (Paus et al., 1999; Gogtay et al., 2004). Because several studies have shown that adolescents are more prone to risk taking, for example substance use, risky sexual behaviour or fast driving (Arnett, 1999; Mcgue & Iacona, 2008; Pfeifer et al., 2011;

Somerville, Jones, & Casey, 2010; Steinberg, 2010), the neural basis of risk taking has been subject to many neuroimaging studies so far.

Neuroimaging studies started to investigate the connection between risk taking behaviour and functional brain differences during reward processing. However, the studies brought conflicting results. On the one hand, some results point to hyposensitivity (Bjork et al., 2004b; Bjork, Smith, Chen, & Hommer, 2010) of the reward system in adolescents compared to adults, i.e. brain activity during the anticipation of a reward is lower in the adolescent than in the adult brain. This hyposensitivity might lead to more extensive risk seeking in the context of reward related behaviour in adolescents. For example one study showed that the reward system in the brain of adolescent smokers is hyposensitive in response to rewards which might support this hypothesis (Peters et al., 2011). To compensate for this hyposensitivity, these individuals might be more prone to smoking initiation. On the other hand, some studies showed hypersensitivity of the adolescent reward system to the anticipation of rewards compared to adults (Ernst et al., 2005; Galvan et al., 2006; Van Leijenhorst et al., 2010). In these studies, the hypersensitivity has been interpreted as a reason for more risk taking behaviour in adolescents. It was proposed that a higher activation in the reward system of the brain leads to engagement in risky behaviour, because higher brain activity in the reward system leads to a stronger feeling of reward in adolescents. Possible reasons for the diverging results like different age of the adolescent participants, different adult comparison groups, different task designs and analyses have already been discussed elsewhere (Galvan, 2010).

One alternative reason which is of special interest for the current thesis is the relation of different task designs to impulsivity. Impulsivity seems to have an influence on brain activity in reward tasks. As mentioned in section 1.2.1 several studies have shown this influence in diverse groups of individuals (Beck et al., 2009; Bjork, Chen, & Hommer, 2012; Buckholtz et al., 2010; Hariri et al., 2006; Scheres et al., 2007). Regarding the task design, studies which

investigated reward processing in adults and adolescents have so far used different tasks. These tasks have some common features. For example, each has the same phases: an anticipation phase, which starts with a cue indicating that a reward could be obtained, a response phase, which requires a response of the subject, and the reception phase, which provides feedback whether a reward was obtained or not. Of a greater importance for the relation between different tasks and impulsivity are the different features of the tasks, such as certainty of rewards and the demands which are required to obtain a reward. For example, there are tasks in which the link between the reward and the requirement to obtain the reward is deterministic. Subjects are aware of the relation between a cue, the requirement to their action and the possible outcome. Therefore, those tasks can be described as tasks with a deterministic payoff. On the other hand, there are tasks which have probabilistic rewards or require learning of cue-reward-relationships during the task. In contrast to tasks with a deterministic payoff, the relation between cue, required action, and possible outcome are not explicitly disclosed to the subject at the beginning of the task. Therefore those tasks can be described as tasks with a stochastic payoff.

Impulsivity has been shown to be differentially related to tasks with different payoffs. For example, it has been shown that more impulsive alcoholics show *hyposensitivity* in the reward system during anticipating deterministic-payoff-rewards (Beck et al., 2009), but that more impulsive adults are *hypersensitive* to rewards in a task with a stochastic payoff (Hariri et al., 2006). This might be a possible explanation why studies which used tasks with a deterministic payoff found a *hyposensitivity* in adolescents compared to adults (Bjork et al., 2004b; Bjork et al., 2010), whereas studies which used tasks with stochastic payoff found results that point to *hypersensitivity* (Ernst et al., 2005; Galvan et al., 2006; Van Leijenhorst et al., 2010) of the reward system in adolescents. The discount rate, as a measure of impulsivity, might be the link between the differences found between adults and adolescents in reward processing,

because adults and adolescents differ in their discounting rates (Green et al., 1994; Green et al., 1999). A possible approach to disentangle age and impulsivity related differences during reward processing might be to use an intertemporal choice task, which makes it possible to adapt the reward values to the individual discount rates.

1.4 Intelligence and its relation to intertemporal choice

As mentioned in section 1.1, intelligence might be a protective factor for disadvantageous health-related behaviour (Jefferis et al., 2003) and is hence one of the subjects in the current thesis. This section will first give a short introduction to intelligence followed by an overview about associations between brain structure and function and intelligence. Finally, findings regarding intelligence and intertemporal choice will be presented.

Intelligence refers to the "ability to understand complex ideas, to adapt effectively to the environment, to learn from experience, to engage in various forms of reasoning, to overcome obstacles by taking thought" (Neisser et al., 1996, p. 77). Intelligence can be measured with the help of intelligence tests. A common intelligence test is the Wechsler Adult Intelligence Scale (Wechsler, 2008) and its German version the Wechsler Intelligenztest für Erwachsene (WIE, von Aster, Neubauer, & Horn, 2007), or for children and adolescents the Wechsler Intelligence Scale for Children (WISC, Wechsler, 2004) and the German version Hamburg Wechsler Intelligenztest für Kinder (HAWIK, Daseking, Petermann, & Petermann, 2007; Petermann & Petermann, 2007), which measure the fluid and crystallised intelligence. Crystallised intelligence refers to acquired knowledge, whereas fluid intelligence refers to the capacity to think logically independent of acquired knowledge. Both are factors of general intelligence (Cattell, 1963; Horn & Cattell, 1966; Li et al., 2004; Lubinski, 2004; Spearman, 1904). A recent comprehensive review about the issue of intelligence can be found elsewhere (Nisbett et al., 2012).

Rindermann *et al*. (2011) investigated several influencing factors of intelligence development in the period from childhood to adolescence. During this period they found an increase in crystallised as well as fluid intelligence, although the increase in crystallised intelligence was higher. Further the increase of intelligence was higher in younger children (6-9 years old) than in older children (10-14 years old) and adolescents (15-18 years old). Moreover, the increase of intelligence was higher when it started at higher level. Cliffordson and Gustafsson (2008) showed that schooling has an even larger impact on the development of intelligence than age. Altogether the findings regarding development show that adolescence seems to be a period in life when intelligence sill develops and that it seems to be influenced by environmental factors, such as education at school.

Neuroscientific research has shown that intelligence is related to structure and function in the brain. The parieto-frontal integration theory (P-FIT) suggests a network consisting of the dorsolateral prefrontal cortex (DLPFC, BA 6, 9, 10, 45, 46, 47), inferior (BA 39, 40) and superior parietal lobe (BA 7), the anterior cingulate cortex (BA 32) as well as regions within the temporal (BAs 21, 37) and occipital (BAs 18, 19) lobes (Jung & Haier, 2007) which is related to intelligence. The theory proposes that the parietal areas of the network are involved in structural symbolism, abstraction, and elaboration and interact with the DLPFC, which serves to test various solutions to a given problem. The ACC then constrains the selected response and inhibits non-selected ones. Regions within the temporal and occipital lobes process visual and auditory input. The theory was further supported by studies (Colom et al., 2009; Johnson, Jung, Colom, & Haier, 2008; Karama et al., 2009) showing that higher scores in fluid and crystallised intelligence were related to higher grey matter volume in these areas. Recently, a higher cortical thickness of the superior frontal cortex has been proposed as common neural basis of intelligence and impulsivity (Schilling et al., 2012). Some studies also show common functional activation patterns (lateral frontal brain areas and parietal brain are-

as) in tasks where performance is highly correlated with Spearman's *g* (e.g. working memory (WM) or problem solving) using positron emission tomography (Duncan et al., 2000) or functional magnetic resonance imaging (fMRI; Waiter et al., 2009). Although tasks where performance is correlated with *g* seem to require more activation especially in frontal and parietal areas of the brain, the association between individual intelligence and brain activity during the task is not entirely clear. Some fMRI studies have shown that more intelligent subjects require less neural resources (i.e. lower blood-oxygen-level-dependent (BOLD) response during the task) during visuo-spatial (Haier, Siegel, Tang, Abel, & Buchsbaum, 1992) or n-back WM tasks (Tang et al., 2010), which is described as neural efficiency. On the other hand more intelligent individuals have been shown using more neural resources in a task comparing simple and complex reasoning (Lee et al., 2006) and during a card sorting task (Graham et al., 2010). These BOLD differences between high and low intelligent subjects were interpreted as functional facilitation (Lee et al., 2006) and different strategies which might have been used by the different groups (Graham et al., 2010). These findings are not necessarily exclusive, because it was proposed that an increase in neural activity in more intelligent subjects manifests especially under conditions like higher difficulty (Gray, Chabris, & Braver, 2003) or more restrictions (Lamm et al., 2001) and is accompanied by better performance. Thus, more intelligent individuals seem to save resources while achieving the same performance and the use of more neural resources seems to lead to better performance.

Regarding intertemporal choices behavioural studies showed that the individual discount rate, as one facet of impulsivity, is related to intelligence. It was shown in several studies that impulsivity is higher in less intelligent adults (de Wit, Flory, Acheson, McCloskey, & Manuck, 2007; Shamosh et al., 2008) and adolescents (Freeney & O'Connell, 2010). Further support for these results comes from a meta-analysis, which has shown a small to moderate inverse correlation between intelligence and impulsivity in intertemporal choice tasks

(Shamosh & Gray, 2008). Regarding the neural underpinnings, Shamosh *et al.* (2008) have shown more brain activity in the anterior prefrontal cortex during a working memory task to be related to higher intelligence (i.e. g-factor) and lower delay discounting, providing indirect evidence. However, no study has reported neural correlates of an intertemporal choice task which are related to intelligence measures.

Brain areas which have been shown to process intertemporal choices largely overlap with regions described in P-FIT (see chapter 1.1). This is consistent since making an intertemporal decision requires the integration of information about two different rewards, to compare them and subsequently to decide. Following the efficiency hypothesis, higher activation in these brain areas which is related to intelligence should lead to differences in performance. Beside the discount rate, consistency of choices, as decision making skill, might be related to intelligence and is hence a possible performance measure. Higher brain activity in these areas might therefore lead to more consistent decisions. But so far there are no studies which have investigated consistency during intertemporal choices in relation to intelligence.

The relation between intelligence and the discount rate might also have an impact on individual health-related behaviour. For example, to reach long term goals of keeping well and fit at older age one has to abdicate consuming cigarettes. The impact of intelligence on health-related behaviour might be mediated by the discount rate. Thus, intelligence might be a protective factor regarding the transition to addiction (Jaroni, Wright, Lerman, & Epstein, 2004; Jefferis et al., 2003).

A better understanding of the neural processes, which underlie the association between intelligence and the behavioural outcomes of intertemporal choices (i.e. discount rate and consistency of choices), would extend our knowledge about possible protecting factors regarding health-related behaviour and related mechanisms in the brain.

1.5 Smoking and nicotine and its relation to intertemporal choice

Smoking and nicotine dependence cause enormous economic costs (in Germany: 18.8 billion Euro per year), especially for health care (in Germany: 5.1 billion Euro per year; see (Steier & Konietzko, 2007). Thus, it is important to find ways to prevent nicotine addiction, help people to quit smoking and prevent the relapse after smoking cessation. To introduce efficient prevention or smoking cessation programs, it is necessary to understand how inter-individual differences influence transition to addiction and cessation success, respectively. The personality trait impulsivity might be one of those inter-individual differences which are related to addiction. Impulsivity has been discussed with regards to many mental health problems (Moeller, Barratt, Dougherty, Schmitz, & Swann, 2001) including substance use disorders. For example, a higher degree in impulsivity has been shown in alcoholics (Bjork et al., 2004a) and in relation to early onset of alcohol use (Nees et al., 2012). Additionally, illicit drug users (Poling, Kosten, & Sofuoglu, 2007), and gamblers (Rodriguez-Jimenez et al., 2006) show higher degrees in impulsivity. More importantly, studies demonstrated the association between smoking and impulsivity (eg. VanderVeen, Cohen, Cukrowicz, & Trotter, 2008).

Studies investigating intertemporal choice revealed higher discount rates for delayed rewards in current smokers than in non-smokers, occasional smokers, and ex-smokers. Discount rates of non-smokers, occasional smokers and ex-smokers did not differ from one another (Bickel et al., 1999; Sweitzer, Donny, Dierker, Flory, & Manuck, 2008). But so far it is unclear, whether the higher discount rate in smokers is due to acute or chronic pharmacological effects of nicotine intake, and if this is either reversible or irreversible. Another explanation for the differences in the discount rate between smokers and non-smokers might be pre-drug group characteristics, i.e. individuals with higher discount rates are more prone to smoking. Higher discounting in young-adult smokers compared to adolescent smokers and non-

smokers indicates the effect of chronic intake of nicotine and might be reversible (Reynolds, 2004). Positive correlations between the discounting rate and the number of daily cigarettes as well as the estimated dose of nicotine have been interpreted as indirect support for a dose-dependent pharmacological effect (Ohmura, Takahashi, & Kitamura, 2005; Reynolds, 2004), but do not preclude steeper discounting as a pre-drug characteristic.

Support for the hypothesis that the effects are reversible comes from findings that show a decrease of discounting in dependent smokers who were reinforced to refrain from smoking for five days (Yi et al., 2008). However, a contrary effect of smoking reduction (and hence nicotine reduction) was shown for shorter nicotine deprivation (13 hours). In this case smoking reduction led to an increase of impulsive choices for monetary rewards (Field, Santarcangelo, Sumnall, Goudie, & Cole, 2006), whereas 24 hours of abstinence did not alter discounting of delayed monetary rewards but of cigarette rewards (Mitchell, 2004). These diverging results could partly be due to different degrees of acute withdrawal symptoms that might additionally affect the discount rate. In order to avoid blending of the effects of withdrawal symptoms and nicotine abstinence, longitudinal studies are needed, investigating abstinent smokers who have passed the phase of acute withdrawal. Another study found no influence of smoking quantity but steeper discounting in smokers with a higher level of nicotine dependence measured with the Fagerström Test for Nicotine Dependence (FTND), supporting the hypotheses that steeper discounting might be either irreversible or a pre-drug characteristic of smokers (Sweitzer et al., 2008). Trait rather than state differences have further been suggested by longitudinal data spanning mid-adolescence to young adulthood (Audrain-McGovern et al., 2009). Temporal discounting was not only stable over time and unaffected by smoking, it even predicted smoking initiation. Moreover, a higher discounting rate was found to be associated with an increased risk for relapse (Goto, Takahashi, Nishimura, & Ida, 2009).

To answer the question whether the effects of nicotine on the discount rate are due to acute or chronic nicotine intake, it would be necessary to study smokers compared to non-smokers. To test acute effects of nicotine non-smokers could be compared under placebo and nicotine. Chronic effects could be revealed by comparing these acute effects with the differences between smokers and non-smokers under nicotine exposure, i.e. the chronic effect of nicotine intake.

1.6 Research objectives and overview about topics

The current work was done to investigate reward related decisions with an intertemporal choice paradigm, which is of relevance for health-related behaviour. The work was focused on the relation between neural processing and individual behavioural measures during the task (i.e. discount rate and consistency of choices). Beside these behavioural measures, other inter-individual differences (i.e. age and intelligence) and the pharmacological effects of acute and chronic nicotine intake were tested. These variables were chosen as examples for risk and protective factors influencing health-related behaviour. They were expected to have an influence on the behavioural measures of intertemporal choices task. Most importantly, the current thesis was done to contribute to a better understanding of neural processes underlying the associations between these risk and protective factors and the behavioural measures.

To investigate age related differences in reward decision making, in *study 1* adults and adolescents were compared in a cross-sectional design. The focus was set on reward value processing and the decision process separately. The discount rate and the consistency of choices were analysed regarding differences between age groups. The study aimed at finding brain behaviour relations, which might be related to age differences in reward dependent decision making.

In *study 2*, intelligence was investigated as a potential protective factor which has been shown to be related to behaviour during intertemporal choice. The associations between the

behavioural measures (discount rate and consistency) and the individual intelligence of adolescent subjects were tested. Additionally, the study aimed at showing whether the associations between intelligence and behaviour were related to common neural processes during intertemporal choice.

To extend the knowledge about the effects of smoking and nicotine on the discount rate regarding the question, whether effects of nicotine are due to acute or chronic intake smokers and non-smokers were investigated in *study 3*. The focus was especially set on differences between smokers and non-smokers reward related decision processing and it was additionally tested whether there was an acute effect of nicotine intake in non-smokers or not. For this purpose, the non-smokers were tested under nicotine exposure and under placebo in a double-blinded, randomised cross-over design.

The overall aim was to investigate different aspects in the field of reward decision making using an intertemporal choice task. As the discount rate as a behavioural measure of the conducted task might be related to health-related behaviour and to mental health problems including substance use disorders (Bickel et al., 2007) and has been proposed to be a trans-disease process (Bickel et al., 2012), it might be fruitful to understand the neural correlates of these measures and relations to risk and protective factors. This would extend the CNDS theory (Bechara, 2005; Bickel et al., 2007; Bickel et al., 2012) regarding brain behaviour relations which might underlie the differences between individuals who experiment with or become addicted to substances and which circumstances support or prevent transition to addiction.

For an overview of the research questions faced by the different studies of the current thesis see Figure 1-1.

1.6.1 Study 1: Reward Processing and Intertemporal Decision Making in Adults and Adolescents: The Role of Impulsivity and Decision Consistency

The study compared reward decision making between adolescents and adults using an intertemporal choice task. The study aimed at finding out whether differences between adults and adolescents in neural processing of reward related decision are due to brain maturation or to differences in behavioural outcome measures like discount rate and consistency of choices.

Questions:

1. Do adults and adolescents differ regarding the behavioural outcome measures (i.e. discount rate and consistency of choices) of intertemporal choice?
2. Do adults and adolescents differ regarding the neural processes of intertemporal choice (reward value processing and decision processing)?
3. How are behavioural outcome measures related to neural processing in intertemporal choice?

Key findings:

1. Adolescents are more impulsive and less consistent in their behaviour during the intertemporal choice task.
2. Neural processing of the value of prospective delayed rewards is more sensitive to the individual discount rate than to chronological age.
3. Lower consistency of intertemporal choices might indicate ongoing maturation of parietal brain areas in adolescents, because BOLD response in these areas was partly related to age as well as to consistency.

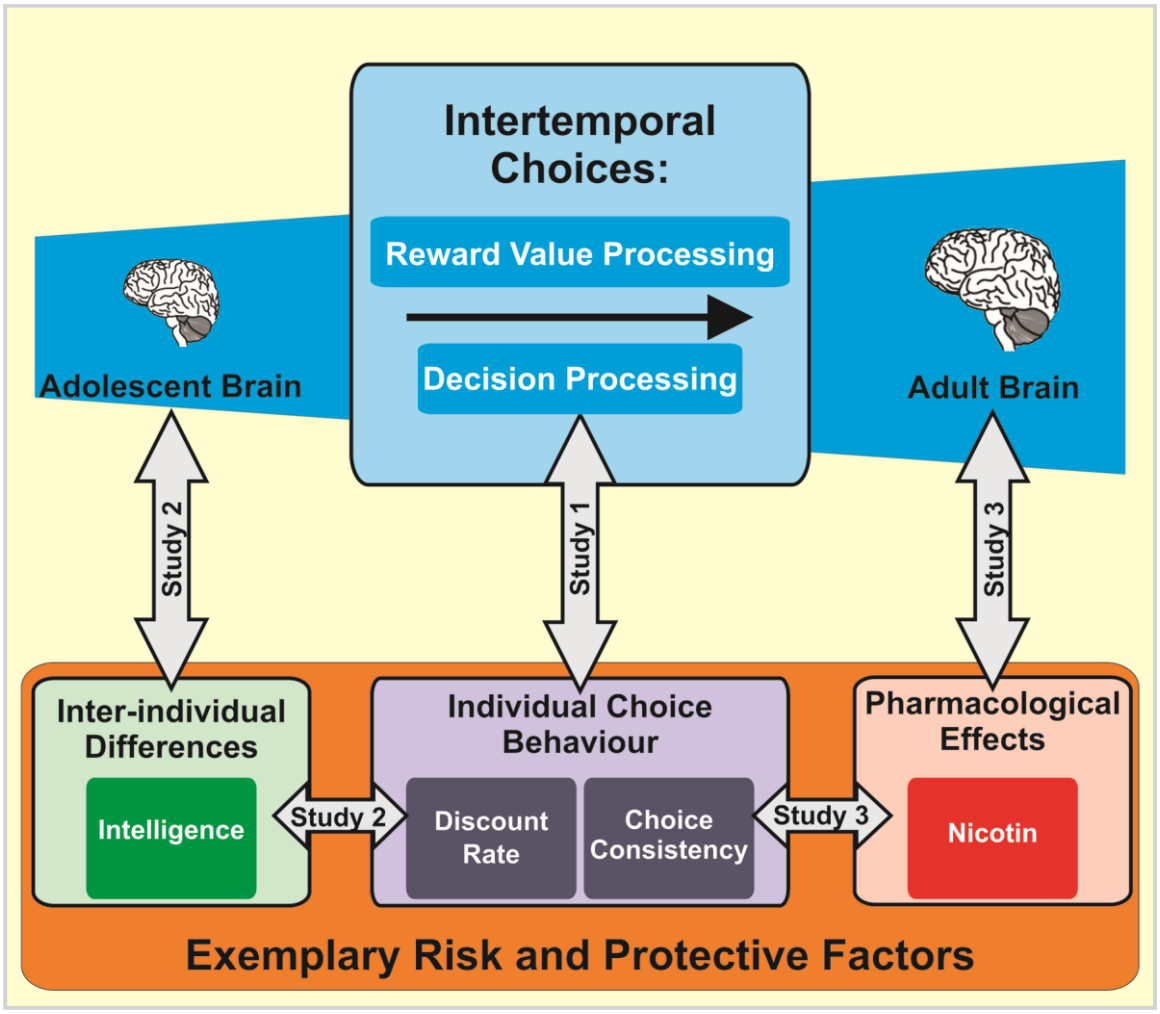

Figure 1-1: Overview about studies conducted for the current thesis. All 3 studies of the thesis investigated the neural processes of intertemporal choices (value processing and decision processing) and the individual choice behaviour. Study 1 investigated the development comparing adolescents and adults. Study 2 investigated the associations with intelligence. Study 3 compared smokers and non-smokers and investigated the effects of a single dose of nicotine in non-smokers.

1.6.2 Study 2: Neural Correlates of Intelligence during Intertemporal Choices in Adolescents

The study was done to test whether possible associations between intelligence and behavioural measures of intertemporal choice (i.e. discount rate and choice consistency) rely on the same BOLD differences during decision making and value processing. Due to the fact that intelligence might be a protective factor regarding the initiation of addictive behaviour and adolescence is the period in life when most people experiment with substances, these associations were tested in adolescent subjects.

Questions:

1. How is intelligence related to behavioural measures of intertemporal choice during adolescence?
2. How is intelligence related to neural processes in intertemporal choice during adolescence?
3. Are the associations between intelligence and behaviour during intertemporal choices mediated by common neural processes underlying intelligence as well as behaviour during the task?

Key findings:

1. Higher scores in the crystallised intelligence measure were related to higher BOLD in the fronto-parietal network during decision making. The higher BOLD signal in this network was related to more consistent decision making.
2. Higher BOLD response in the frontal network during processing of delayed reward value was associated with a lower discount rate and higher crystallised intelligence scores.
3. Parental education as an environmental factor was positively correlated to the offspring's individual crystallised intelligence and negatively to the discount rate. This might implicate that environmental factors in this case act via the association between crystallised intelligence and discounting rates and the overlapping neural correlates.

1.6.3 Study 3: Acute and Chronic Nicotine Effects on Behaviour and Brain Activation during Intertemporal Decision Making

The study compared delay discounting in smokers and non-smokers. Nicotine administration in the non-smoker group following a double-blind cross-over design was done to test whether effects of smoking are primarily due to acute or chronic intake of nicotine.

Questions:

1. Are there behavioural differences in delay discounting between smokers and non-smokers?
2. Are these potential differences related to differences in neural processing of intertemporal decisions?
3. Are these potential differences in neural processing due to acute pharmacological effects of nicotine?

Key findings:

1. Non-smokers were less impulsive than smokers, whereas nicotine administration in non-smokers did not affect their discount rate.
2. Non-smokers showed higher BOLD response during decision making than smokers in a parietal network of the brain, which has been shown to be related to decision making in previous studies.
3. Although acute nicotine administration had no effect on intertemporal choice behaviour, its effects on the BOLD were similar but less pronounced to those observed in smokers compared to non-smokers.

2 Study 1: Reward Processing and Intertemporal Decision Making in Adults and Adolescents: The Role of Impulsivity and Decision Consistency

2.1 Introduction

Reward processing and decision making are core elements of human life and are closely related to risk taking behaviour and impulsivity (Bechara & Damasio, 2002; Bechara, Dolan, & Hindes, 2002; Romer et al., 2009). For example, individuals with high levels of impulsivity (e.g. discounting behaviour) have an increased liability to disorders connected to aberrant reward processing and reinforcement learning such as substance use disorders (Bickel et al., 1999; Bühler et al., 2010; Kirby, Petry, & Bickel, 1999; Reynolds, Patak, & Shroff, 2007) or pathological gambling behaviour (Holt et al., 2003). The link between reward processing, impulsivity and risk taking is also important for developmental studies as it is well known that adults and adolescents differ in risk taking (Arnett, 1999; Chambers & Potenza, 2003).

Brain imaging studies that focussed on developmental aspects of reward processing offered different explanations for risky adolescent behaviour. On the one hand, it was hypothesised that lower activation (i.e. hyposensitivity) in the reward system of adolescents compared to adults may lead to more extensive reward seeking in adolescence (Spear, 2000). On the other hand, higher activation (i.e. hypersensitivity) in the reward system has been hypothesised to lead to an increase in risk taking behaviour (Ernst, Romeo, & Andersen, 2009). Bjork *et al.* (2004b; 2010) found the adolescents' reward system, especially the ventral stria-

tum (VS), to be hyposensitive compared to adults whereas others found hypersensitivity of the VS (Ernst et al., 2005; Galvan et al., 2006; Van Leijenhorst et al., 2010).

Experimental tasks investigating reward processing usually consist of trials containing different phases: The anticipation phase, which starts with a cue indicating that a reward could be obtained, a response phase, which requires a response of the subject and the reception phase, which provides feedback, whether a reward was obtained or not. One reason for the diverging results might be related to the fact that previous studies analysed different phases of experimental trials or the entire trial. But even studies which compared the processing of anticipation and receipt of rewards did not find consistent activation patterns that could explain the differing results comparing adults and adolescents (Bjork et al., 2010; Geier, Terwilliger, Teslovich, Velanova, & Luna, 2010).

Another explanation might be differences in the experimental tasks. All studies that found hyposensitivity (Bjork et al., 2004b; 2010) used a task where subjects received a certain reward, if they responded quickly. During this kind of task subjects are aware of the link between reward cue and reward magnitude and the required response. Thus, there is a deterministic payoff. Two of the three studies that reported hypersensitivity of the reward system used probabilistic rewards (Ernst et al., 2005; Van Leijenhorst et al., 2010) and the third study used a task which required learning of the relation between the reward cue and the reward magnitude (Galvan et al., 2006). In these tasks the link between reward cue, reward magnitude and response is not obvious to the subjects and therefore there is a stochastic payoff.

A third possible explanation linked to the second, is that diverse tasks (those with a deterministic payoff or those with a stochastic payoff) might be differently related to temporal discounting behaviour as one measure of impulsivity. In tasks with deterministic payoffs hyposensitivity of the ventral striatum was shown in more impulsive subjects, e.g. adolescents (Bjork et al., 2004b; 2010), smokers (Peters et al., 2011), adolescents with ADHD (Scheres et

al., 2007) and detoxified alcoholics (Beck et al., 2009). Thus, it seems most likely that higher impulsivity is related to hyposensitivity in the reward system in the case of tasks with a deterministic payoff.

The activation in reward processing areas of the brain (e.g. VS) is positively associated with the magnitude and probability of the stochastic reward while anticipating it (Knutson, Taylor, Kaufman, Peterson, & Glover, 2005). As more impulsive subjects are less risk aversive and discount probabilistic rewards less steeply than less impulsive subjects, the value of an uncertain reward seems to be higher for them. As it was shown by Hariri *et al.* (2006), who found that temporal discounting, which is a measure of impulsivity, is positively related to VS activity in a card guessing game, one could deduce that the VS of impulsive subjects is hypersensitive to stochastic rewards.

However, the whole story might be more complicated, if we consider different measures of impulsivity. Buckholtz *et al.* (2010) as well as Bjork *et al.* (2012) found positive correlations between impulsivity and VS activity in a task with a deterministic payoff scheme. They measured impulsivity with the psychopathic personality inventory (PPI) and hence, tested rather the effect of the impulsive antisocial trait construct (Buckholtz et al., 2010). Another study, using an impulsivity questionnaire, even found no effects of impulsivity (Galvan, Hare, Voss, Glover, & Casey, 2007).

The link between impulsivity and neural correlates of reward processing has been shown more directly by using intertemporal choice tasks. In these tasks subjects have to choose between a smaller reward delivered immediately or soon and a larger reward delivered later. More impulsive individuals discount delayed rewards more steeply and accordingly prefer immediate rewards. Imaging studies in humans using intertemporal choice tasks found that activation in the VS, mPFC and posterior cingulate cortex (PCC) reflects the subjective value of rewards in adults (Kable & Glimcher, 2007; Peters & Buchel, 2009) and is associated

with subjects' decisions (Hariri et al., 2006; McClure et al., 2004). It should be noted that this measure of discounting behaviour only reflects one facet of impulsivity. Another behavioural facet of impulsivity is the ability to inhibit a prepotent motor response, measured via stop-signal tasks (Logan et al., 1997; Bedard et al., 2002). In addition, there are several questionnaires that measure facets of impulsivity. However, these different measures are not necessarily highly correlated (Reynolds et al., 2006). This paper focusses on discounting behaviour as it has been shown as directly linked to reward processing (Kable & Glimcher, 2007; Peters & Buchel, 2009).

Taken together it has been shown that impulsivity is related to neural correlates of reward processing and also influences evaluation of rewards on a behavioural level (Kirby & Herrnstein, 1995; Kirby & Marakovic, 1995; Kirby et al., 1999). Regarding discounting behaviour in intertemporal choice tasks in adults and adolescents, it has been shown that adolescents were more impulsive (Green et al., 1994; 1999). Therefore, when comparing reward processing between both groups it is important to account for individual impulsivity (e.g. by individual adaptation of stimuli or by including it as a covariate). However, previous studies which compared adolescents and adults regarding reward processing have not done this (Bjork et al., 2004b; 2010; Ernst et al., 2005; Galvan et al., 2006; Van Leijenhorst et al., 2010). Adapting the monetary rewards to individual discounting behaviour might possibly wash out differences between adults and adolescents, which would show that the previous reported differences between adults and adolescents were caused by individual discounting behaviour.

Alongside reward value processing during intertemporal choice there is also the decision processing phase. This phase refers to the process of comparing both alternatives presented in a given trial. The phase is associated with brain activation in the parietal cortex, the dorsolateral prefrontal cortex and the lateral orbitofrontal cortex as well as the visual cortex

and premotor areas (McClure et al., 2004) and is distinct from the evaluation of value. Both processes run in parallel. Decisions influenced by discounting behaviour might be more or less consistent. Consistency here refers to the degree to which subjects choose the alternative with the higher subjective value over the time course of the task. Thus, consistency is related to the comparison of the two options (decision processing) whereas discounting behaviour is related to the evaluation of the offered rewards (reward value processing). Consistency might be a further behavioural measure which influences subjects' decisions. To our knowledge there is no study which analysed consistency of decisions with imaging methods.

In this study we compared intertemporal choices in adults and adolescents. This kind of task allowed us to measure discounting behaviour as one aspect of impulsivity as well as reward processing on the neuronal level. In a pre-scan training session we could assess individual discounting rates and with the help of that adapt the monetary rewards subject-wise. This was done to make sure that possible results are not influenced by the discounting-dependent perception of rewards. During the scanning session we offered a series of delayed rewards which could be either accepted or rejected by the subject. In case of rejection the subjects received a lower but immediate reward which was fixed in each trial and presented to the subject before the scanning session started. The adaptation was done to present subjectively equivalent valued rewards across all subjects and promote a 50% rate of acceptance. To ensure realistic choices and increase task relevance (Zink, Pagnoni, Martin-Skurski, Chappelow, & Berns, 2004), we informed the participants that one of their choices would be selected by chance and paid exactly at the respective time point.

We expected to clarify whether areas of the brain which are involved in reward value processing of delayed rewards are hypo- or hypersensitive in adults compared to adolescents (Q1) and whether temporal discounting behaviour as one measure of impulsivity is associated with neural processing of the value of monetary rewards (Q2). Additionally, we wanted to test

whether adults and adolescents show differences in brain response during the decision processing phase in intertemporal choice (Q3) and whether the consistency of choices is related to brain activity during the decision making phase in general (Q4).

2.2 Method

2.2.1 Subjects

The acquisition of data from adolescents was part of the project "The adolescent brain", which is funded by the German Federal Ministry of Education and Research (BMBF). 260 adolescent subjects and one of their legal guardians signed informed consent and were invited to take part in the study. They received monetary compensation for their participation. 235 of them (122 males, mean age: 14.6, SD = 0.3, min: 13.7, max: 15.5) participated in the two parts of the experiment (training session and imaging session). They received additional monetary compensation depending on their decisions during the task (see section 4.2.). The control group consisted of 28 undergraduate students of the Technische Universität Dresden (TU Dresden) and one subject from a subject pool (15 males, mean age: 25.0, SD = 5.8, min = 19.0, max = 50.4). The study was approved by the institutional ethics committee of the Faculty of Medicine at the TU Dresden. All participants in the control group provided written informed consent prior to examination and received monetary compensation which was depending on their decisions during the task (see section 4.2.). The compensation for the task ranged from 5 to 35 Euro.

All subjects with mental disorders, including substance use disorder were excluded from the sample. For assessment of all adolescent subjects we applied the Development and Well-Being Assessment (DAWBA, Goodman, Ford, Richards, Gatward, & Meltzer, 2000), as it is a well validated questionnaire for children and adolescents from age 5 to 17. For adults we applied either the Structured clinical Interview for DSM-IV (Strukturiertes Klinisches In-

terview für DSM-IV (SKID), Wittchen, Zaudig, & Fydrich, 1997) or the computerized version (Composite International Diagnostic Interview (Composite International Diagnostic Interview (CIDI), Robins et al., 1988). As we used data of these interviews only to exclude subjects with mental disorders, we think that using different measures is not a limitation in our case. All participants had normal or corrected to normal vision. The final data analysis included 195 adolescent subjects and 27 adult subjects. Seven of the adolescent datasets were incomplete due to technical difficulties during the imaging session and the data of 10 further adolescents and 1 adult were excluded due to signal drop out. 23 of the adolescent subjects and one of the adult subjects were removed from the sample because of the number of invalid choices during the imaging session of the experiment (see behavioural data analysis section (2.2.4)).

The project "The adolescent brain" aims to investigate structural and functional brain development in the context of environmental and genetic factors. The study has a longitudinal design and seeks to reveal links between functional as well as structural brain development and liability for substance use disorders. For that purpose, participants complete questionnaires regarding personality, substance use, leisure time activities and well-being. Furthermore they accomplish several experimental functional magnetic resonance imaging (fMRI) tasks. Additionally, participants' parents answer questionnaires about themselves, their family background and their offspring. Participants are assessed using the same tools again after 2 years (mean age 14, 16 and 18). Adolescent subjects were recruited via school visits in the Dresden school district.

The adolescent data presented here were part of the longitudinal study described above. We present results of the first wave of adolescent data in a cross-sectional design compared to data of an adult group. We collected the data of 29 adults to have a comparison group for the first wave of adolescent data. Hence, the notable difference in sample sizes.

2.2.2 Task

The intertemporal choice task used in our study consisted of two sessions. First, the training session was performed outside the MRI scanner and served to estimate individual discount rate as well as to train the participant for the subsequent imaging session. In order to give the participants time to understand the task and response procedure, the first 3 trials in the training session were not included in the behavioural analysis. After these three trials, each participant underwent 50 behavioural decision trials. In each of the trials subjects had to choose either a small immediate amount of money or a larger amount of money paid after a delay. Before the task started, we instructed the participants that the immediate amount would be 20 Euros in every trial. At the beginning of each trial, subjects saw the amount and delay of money being delivered later. After 2 seconds, subjects had to indicate their preference by pressing either the left button (for the later alternative) or the right button (for the immediate option). Directly after their response, subjects received feedback on the amount and delay chosen (either of the immediate or later reward) to ensure that participants could monitor their decisions. For each of the five delays (10, 30, 60, 120 or 180 days), subjects had to make 10 decisions. After 10 trials, the delay changed for the next 10 decisions. The training session was adaptive, i.e. the amounts of money displayed increased or decreased based on the subject's decision in the previous trial. For instance, if the immediate amount was chosen, for the next trial the delayed amount increased half the difference between immediate and delayed reward and vice versa. Based on the choices in these 50 trials, we estimated the individual discount parameter *k*. First, we estimated the indifference amount for each of the five delays, i.e. the mean of the maximum delayed amount rejected and the minimum delayed amount chosen. The indifference amount represents the amount (*A*) in the hyperbolic function:

$$V = \frac{A}{1 + k \times D}$$

Further, in this function *V* represents the subjective value of a reward (during our training session it was 20 Euro), *D* the delay, and *k* the individual discount parameter. Parameter *k* was estimated to best fit the hyperbolic curve consisting of 6 points, i.e. 20 Euros for a delay of 0 (immediate reward) and the indifference amounts of the 5 delays using ordinary least square. We used a hyperbolic function, because previous studies found that it best fits the data (Kirby & Marakovic, 1995; Simpson & Vuchinich, 2000).

We adapted the intertemporal choices presented during the imaging session of the task to the individual level of impulsivity (*k*) in a way that (1) subjects ought to choose the immediate reward in 50% of trials, (2) the mean value (*V*) of all delayed rewards would be the same (30 Euro) for each subject, and (3) the maximal value (*V*) of all rewards was twentyfold the minimum value.

The delays (*D*) were the same as in the training session of the experiment, i.e. 10, 30, 60, 120, 180 days. For each of the 5 delays we computed 18 values (9 higher than the individual immediate amount and 9 lower than the individual immediate one) using the following formula:

$$V_d = V_0 \times \frac{1 + (k \times D \times c)}{1 + (k \times D)}.$$

The parameter *c* was set to 0.1, 0.15, 0.20, 0.25, 0.30, 0.35, 0.4, 0.45 and 0.50 to ensure that for all values (V_d) lower than the immediate reward the respective delayed amounts were always higher than the immediate ones (because choosing between 20 Euro now and 15 Euro in 10 days would not contain any information regarding decision preferences). To ensure the same range for each participant, the maximum value (*V*) for each delay was exactly twentyfold the lowest value (*V*) for the 180 days (*D*) condition (i.e. minimum value for each subject). The difference between immediate reward and maximum reward value (*V*) was divided

into 9 equidistant value categories above the immediate reward. The mean of all computed values (*V*) was standardized to 30 Euro. Finally, all respective amounts (*A*) were computed using the formula:

$$A = V + (V \times k \times D).$$

Pairs of amounts and delays were computed in advance (for two sample sets see Table S 1) and presented in random order during the imaging session of the experiment. The immediate amount was also adapted for each participant so that rewards were presented with the same mean over all trials for each subject. So the immediate reward differed from 20 Euro during the training session, but was the same in all trials. The delayed larger amount and the respective delay were presented for 2 seconds (Figure 2-1).

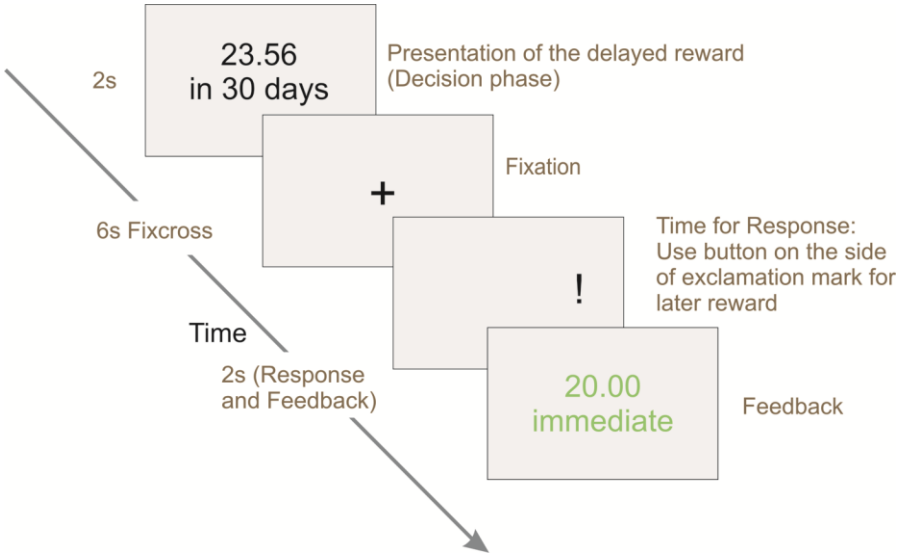

Figure 2-1: Timecourse of each of the 90 fMRI trials.

After a further period of 6 seconds during which a fixation cross was displayed, the response timeframe (2 seconds) started. An exclamation mark on the left or right side of the screen indicated to the participant which button was mapped onto the larger delayed amount. In order to avoid lateralization effects of response, in fifty percent of the trials the decision for the delayed reward was mapped to the right button and in fifty percent of the trials to the left one. Each trial of the experiment ended with feedback of the participants' decision (amount

and delay was shown) followed by an inter-trial-interval (ITI) with a duration of seven seconds on average (uniform distribution). The whole session (90 trials) lasted 25 minutes.

The participants were told that one of their choices was selected by chance and paid exactly in 10, 30, 60, 120 or 180 days via bank transfer or immediately after scanning. We integrated this procedure to ensure that participants made realistic choices and to increase task relevance (Zink et al., 2004).

2.2.3 MRI data acquisition

Scanning was performed with a 3 T whole-body MR tomograph (Magnetom TRIO, Siemens, Erlangen, Germany) equipped with a standard head coil. For functional imaging, a standard Echo Planar Imaging (EPI) Sequence was used (repetition time (TR): 2410 ms; echo time (TE): 25 ms; flip angle: 80°). fMRI scans were obtained from 42 transversal slices, orientated 30° clockwise to the anterior commissure–posterior commissure line, with a thickness of 2 mm (1 mm gap), a field of view (FOV) of 192 x 192 mm and an in-plane resolution of 64 x 64 pixels, resulting in a voxel size of 3 x 3 x 3 mm. To exclude structural abnormalities, a 3D T1-weighted magnetization-prepared rapid gradient echo (MPRAGE) image data set was acquired (TR = 1900 ms, TE = 2.26 ms, FOV = 256 x 256 mm, 176 slices, 1 x 1 x 1 mm^3 voxel size, flip angle = 9°). Images were presented via NNL goggles (Nordic Neurolab, Bergen, Norway). Task presentation and recording of the behavioural responses was performed using Presentation® software (version 11.1, Neurobehavioral Systems, Inc., Albany, CA).

2.2.4 Behavioural data analysis

We estimated the discount parameter, *k*, for each subject from the data of the initial training session of the experiment using MATLAB 7.1. For group comparisons regarding the impulsivity we compared the log-transformed *k*-parameter, because of its deviance from normal distribution.

To check the quality of the subjects' decisions during the fMRI part of the task, we also analysed the consistency of subjects' responses which might be related to impulsivity. Consistency here denotes the degree to which subjects choose the alternative with the higher subjective value. To compute a parameter for the subjective consistency we ran a Receiver Operating Characteristics curve (ROC curve) analysis with subjective value of the delayed reward as a predictor for the respective choice. For each subject, we computed the area under the curve (*AUC*) as a consistency parameter, which was supposed to be higher for more consistent subjects (i.e. always choosing the reward with the higher value results in an *AUC* of 1; complete randomness of choices would yield an *AUC* of 0.5). Statistical testing and determination of *AUC* was computed with SPSS 17. All statistical tests regarding *AUC* were done with the rank-transformed *AUC* (*rank_AUC*), because the *AUC* values were not normally distributed.

Trials with implausible decisions based on analysis of the behavioural data from the imaging session (i.e. trials with a decision for a reward with a subjective value lower than half of the alternative reward) and trials without response (missing trial) were regarded as invalid. For all analyses we only included subjects with more than 80 valid trials. This criterion applied to 195 adolescents and 27 adults. To verify the exclusion criteria we compared the *AUC* of included and excluded subjects. The median was higher for the included subjects (Md=0.947) than in for the excluded (Md=0.879). The difference, statistically tested with *rank_AUC* was significant ($T=3.684$, $p<0.01$).

A further behavioural measure was the subject's mean reaction time (*RT*) of pressing the response button after the response time frame started during the imaging session. We analysed the group differences using a T-test. Additionally, we tested whether reaction time was associated with the measure of impulsivity (*k*) or consistency (*AUC*).

2.2.5 MRI data analysis

We analysed functional MRI data using statistical parametric mapping (SPM 5, Wellcome Department of Neuroimaging, London, United Kingdom). For preprocessing, the data of 636 volumes were corrected for temporal differences in scantime to minimize temporal differences in slice acquisition and inter-scan head motions over the course of the session. The scans were normalized to the standard EPI template (Montreal Neurological Institute (MNI)) and smoothed using an isotropic Gaussian kernel (8 mm full-width at half-maximum).

For first level data analysis we used two different models. The first model was for testing processing of reward value (Q1) and the decision making process (Q3 and Q4). It consisted of four regressors for different events of valid trials: For all these trials, the decision making phase (presentation of the delayed reward) and the subsequent motor response/feedback (separated for responses with the left and right hand) were modelled as events using the canonical hemodynamic response function (HRF). The subjective reward value (computed with the subjective impulsivity parameter, *k*, from the initial training session of the experiment) of each delayed reward presented was additionally included as parametric modulation of the respective event. The presentation of the delayed reward of invalid trials was modelled as a further regressor. For trials with implausible choices, the subsequent motor response was modelled using the same regressor as in valid trials. To alleviate the effects of subjects' movement, we integrated the six realignment parameters (three translation and three rotation parameters) as regressors of no interest.

The second first level model was done to test the hypothesis, whether the network tracking the reward value is hyposensitive in impulsive subjects (Q2). We performed the same first level analysis as described before, but this time used a fixed discounting parameter *k* for all subjects to compute the value of the delayed reward used for parametric modulation. This was done to preserve differences in reward processing related to subjective impulsivity. We

chose the median *k* of all subjects (*k* = 0.01) as fixed discounting parameter because we wanted the same number of subjects with individual discount parameters (*k*) either higher or lower than the fixed one.

For second level analysis we excluded the 24 subjects who showed 10 or more invalid trials out of 90 trials (see behavioural data analysis section). This was done to ensure that the included subjects did the task properly.

To analyse the group differences between adults and adolescents regarding the neural effects of reward value (Q1) and intertemporal decision making (Q3) we ran two independent 2-sample t-tests. As dependent variable we used the beta coefficients computed for the parametric modulation of the decision event with the individually adapted reward value (Q1; first level model 1) and accordingly the mean activation during the decision event (Q3). To further ensure that the group comparison was not confounded by individual differences in impulsivity, we added the log-transformed discount parameter *k* as a covariate to this second level model. We log-transformed this covariate because of its deviance from normal distribution.

To assess whether the discount parameter, *k*, influenced the BOLD response related to value processing based on the fixed impulsivity (Q2; model 2), a regression model was specified with the effect of the reward value (based on the fixed discount parameter) and the discount parameter *k* as a covariate.

To test whether BOLD response during intertemporal decision phase was influenced by the consistency (*AUC*) of choices (Q4), we ran a further regression on the effect of the decision event with consistency (*AUC*) as covariate. The *AUC* values were rank-transformed, because they were not normally distributed.

Main effects regarding brain activity related to processing the reward value (1) and during intertemporal choice (3) were analysed with whole brain analysis. Statistical thresholds for all analyses were set to $p < 0.05$ (FDR corrected) in at least 25 contiguous voxels. To pre-

sent the results regarding the value processing and the decision phase more clearly the threshold was set to $T > 3.13$ ($p = 10^{-3}$) and $T > 4.35$ ($p = 10^{-5}$) respectively.

Based on this, we then restricted both group comparisons and both regression analyses to the areas found for the respective main effect (i.e. effect of reward value (F-contrast; $p<2*10^{-3}$, uncorrected), effect of intertemporal decision making (F-contrast; $p<2*10^{-5}$, uncorrected). F-contrasts were chosen to have a mask that covers all regions where activation was positively or negatively correlated with the respective main effect. The threshold was set to twice the threshold as for the t-contrasts in either one or the other direction to keep it equivalent.

2.3 Results

2.3.1 Behavioural results

During the training session of the experiment, the overall median discount parameter was Md(k) = 0.01 (min(k) = 0.00009, max(k) = 0.0749). Adolescents showed a median discounting parameter of Md(k) = 0.01. This parameter ranged from 0.000738 for the least impulsive to 0.0703 for the most impulsive adolescent. The adult participants showed a median discounting parameter of Md(k) = 0.0064 (least impulsive: 0.00009, most impulsive: 0.0749). As reported by former studies, the adults discounted delayed rewards less steeply than the adolescents ($T = 2.377$, $p < 0.05$). Please note that statistical testing was done with log-transformed values, because the k values were not normally distributed.

One aim was to individually adapt the task and to obtain equally frequent decisions for either the immediate or the later reward in each subject. During the imaging session, subjects preferred the immediate reward in 50.30% (SD = 8.76) of trials, indicating successful matching of monetary rewards. Regarding these decisions, we found no differences between adoles-

cents and adults. Checking the consistency of choice behaviour via ROC curve analysis revealed that adults (Md(*AUC*) = 0.956) were more consistent in their decisions (T = 2.124, p < 0.05) than adolescents (Md(*AUC*) = 0.944). For the analysis of these data we used the rank-transformed AUC values (*rank_AUC*). Additionally, there was no significant correlation between subjects' discounting parameter *k* (*log_k*) and consistency of choices (*rank_AUC*; r = -0.048, p = 0.293). Analysis of reaction time revealed no differences between groups (Adolescents: M = 630.0, SD = 10.0; Adults: M = 620.0, SD = 10.0; T = 0.551, p = 0.585). There was neither an association with impulsivity (*log_k*, r = 0.12) nor consistency (*rank_AUC*, r = 0.033).

2.3.2 Imaging results

2.3.2.1 Reward value based processing (group comparison, Q1)

The parametric analysis over all subjects revealed a substantial positive correlation of the value of the delayed reward option and BOLD response in ventral striatum (VS), PCC and mPFC (Figure 2-2a). The beta coefficients related to value processing did not differ between adolescents and adults in the VS, mPFC and PCC, as shown in Figure 2-2b. Statistical testing of group differences in all 3346 voxels found for the main effect of reward value processing revealed no difference regarding value processing. Results are presented separately for the whole group (Table S 2) as well as for adolescents (Table S 3) and adults (Table S 4).

2.3.2.2 Associaton of Impulsivity (k) with reward value processing (Q2)

Based on first level statistics assuming the same impulsivity (*k*) for each subject we found an inverse correlation between log-transformed *k* and brain activation on the borders of the ventral striatum (Table S 5). The analysis was restricted to brain areas where a robust main effect for reward value processing (3346 voxel) occured.

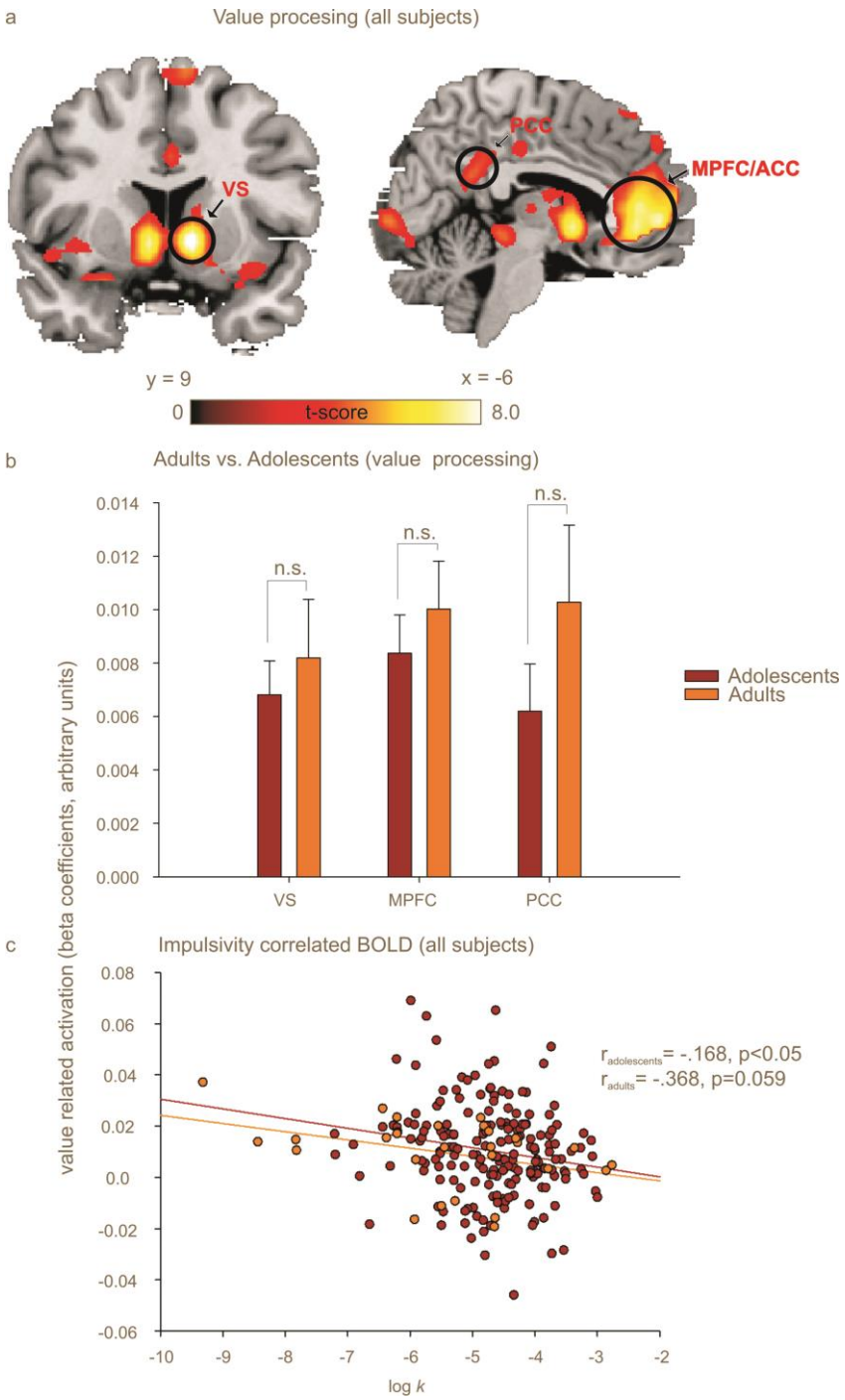

Figure 2-2: Value processing in the adolescent and the adult brain. 2.2a: Brain regions where BOLD response is correlated with magnitude of reward value (red; threshold t = 3.13; p < 10-3 and at least p < 0.05, FDR-corrected in 25 contiguous voxels) in all subjects. 2.2b: Mean activation in the value processing areas in adults and adolescents based on the subjective value model (model 1); no group differences were observed (p > 0.05) in functional ROIs based on value related activation in ventral striatum (VS), medial prefrontal cortex (MPFC) and posterior cingulate cortex (PCC); errorbars indicate SEM. 2.2c: Value related BOLD averaged over left and right ventral striatum (VS) (functional ROI: 5mm sphere around 9 6 -3 and -9 6 -6) based on fixed k model in adolescents (dark red) and adults (orange). Correlations did not differ between adolescents and adults (Z = 0.952, p = 0.341).

To analyse the activation in the ventral striatum more precisely, we additionally performed a post-hoc ROI analysis. For that purpose we extracted the signal change in a functional ROI of the left and right ventral striatum, i.e. a 5mm sphere around the value related peak activation (9 6 -3 and -9 6 -6) and correlated it with the log-transformed discount parameter *k*. This analysis revealed an inverse association of the impulsivity (*log k*) and the signal change in the left and right ventral striatum in adolescents as well as in adults (Figure 2-2c). Although the correlation in adults was higher (r_{adults} = -0.368, $r_{adolescents}$ = -0.168), there was no significant difference between groups (Z = 0.952, p = 0.341).

2.3.2.3 Processing during intertemporal decision making (group comparison, Q3)

A whole brain analysis over all subjects revealed that presentation of the potential later reward (decision phase) independent of value elicited brain activity in visual areas (dorsal and ventral stream), striatum, pre-motor areas, cingular gyrus and frontal parts of the brain, like BA8, dorsolateral prefrontal cortex (DLPFC) and ACC (Figure 2-3a).

Table 2-1: Comparison of BOLD (adults>adolescents) during decision making (Threshold t = 3.13; p = 10-3 and at least p<0.05, FDR-corrected in 25 contiguous voxels)

Anatomical area	**Hem.**	**Size**	**Coordinates**			**FDR corrected p-value**	**Z_{max}**
		(voxels)	**x**	**y**	**z**		
Parietal Lobe: Precuneus	R	341	3	-60	60	< 0.001	6.12
Superior Parietal Lobule (BA7)	L		-36	-69	51	0.008	3.98
Superior Parietal Lobule (BA7)	R		6	-69	57	< 0.001	5.47
Medial Frontal Gyrus (BA6)	L		-6	-30	75	0.002	4.63
Inferior Parietal Lobule (BA40)	L	96	-45	-60	48	0.007	4.07
Inferior Parietal Lobule (BA40)	R	107	45	-54	51	< 0.001	5.28
Temporal Lobe: Fusiform Gyrus	R	40	24	-78	-21	0.028	3.5

Statistical analysis, restricted to the 26830 voxels found for the main effect, revealed that adults compared to adolescents showed more activation (Figure 2-3b, Table 2-1) in left superior and left and right inferior parietal cortex (BA7 and BA40) and left temporal cortex (BA37). Separate results for the whole group, adolescents and adults can be found in Table S 6, Table S 7 and Table S 8, respectively.

Table 2-2: Consistency (rank AUC) related BOLD during the decision making process (Threshold t = 3.13; p = 10-3 and at least p<0.05, FDR-corrected in 25 contiguous voxels)

Anatomical area	Hem.	Size (voxels)	Coordinates x	y	z	FDR corrected p-value	Z_{max}
Parietal Lobe: Precuneus	L	76	-3	-75	51	0.009	4.19
Parietal Lobe: Precuneus	R		6	-75	36	0.024	3.33
Superior Parietal Lobule (BA7)	L	37	-36	-63	51	0.015	3.66
Inferior Parietal Lobule (BA40)	L		-39	-51	45	0.023	3.38
Inferior Parietal Lobule (BA40)	R	36	39	-54	48	0.013	3.81
Middle Frontal Gyrus (BA9)	L	28	-51	24	36	0.009	4.18
Inferior Frontal Gyrus (BA45)	L		-57	21	21	0.022	3.40
Middle Frontal Gyrus (BA9)	R	31	51	30	33	0.009	4.54
Middle Frontal Gyrus (BA46)	R		48	42	24	0.020	3.50
Temporal Lobe: Fusiform Gyrus	L	29	-51	-48	-15	0.014	3.75
Middle Temporal Gyrus	L		-57	-45	-9	0.020	3.49
Parahippocampal Gyrus	R	54	18	-45	0	0.009	4.65
Thalamus	L	327	-21	-33	3	0.009	4.86
Thalamus	R	208	18	-12	12	0.009	4.39
Putamen, Lentiform Nucleus	R		30	-15	9	0.012	3.92
Posterior Cingulate (BA30)	R	31	12	-63	6	0.015	3.67
Posterior Cingulate (BA30)	R		15	-60	15	0.020	3.47

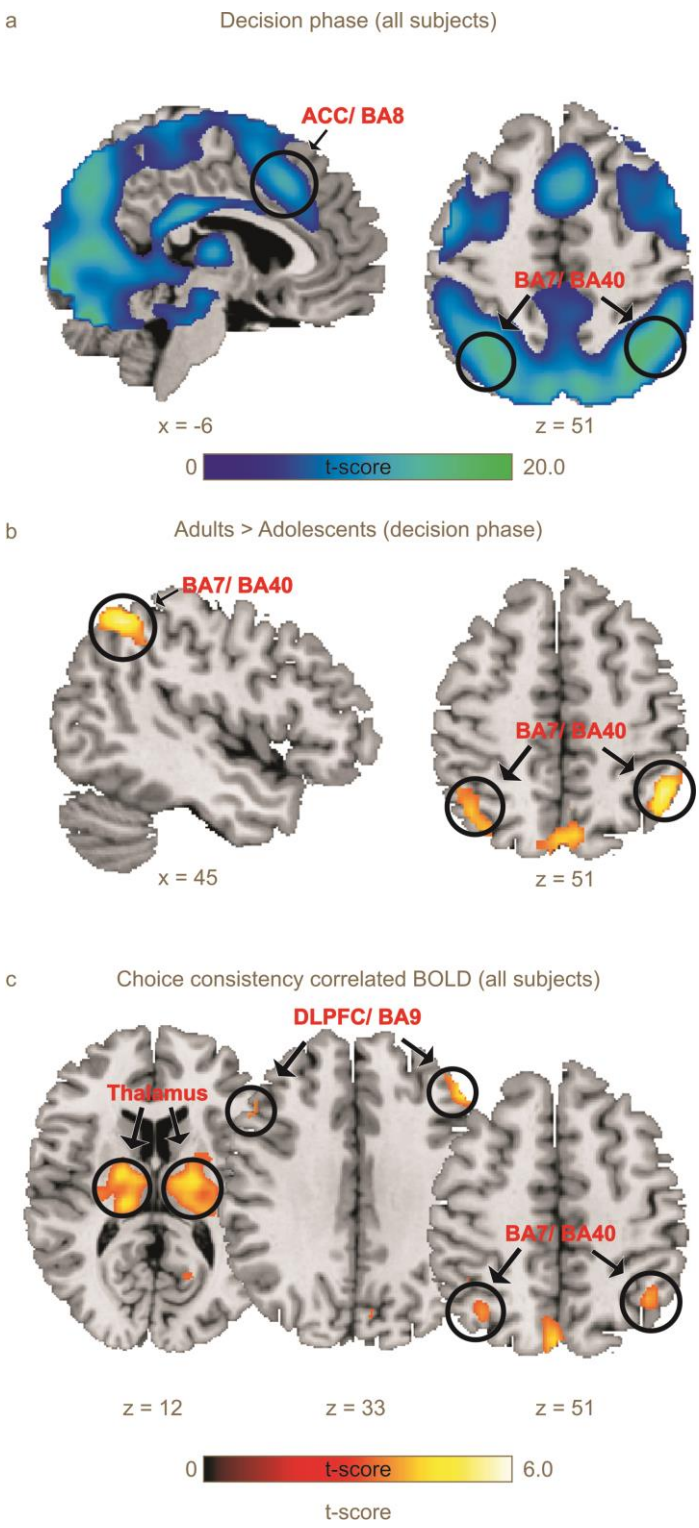

Figure 2-3: Decision processing in the adolescent and the adult brain.2.2a: Brain regions active during inter-temporal decision making (blue; threshold t = 4.35; $p < 10^{-5}$ and at least $p < 0.05$, FDR-corrected in 25 contiguous voxels) 2.2b: Areas, which are more activated in adults than in adolescents during inter-temporal decision making (decision phase). 2.2c: Areas where BOLD response is correlated with the consistency of choice in adolescents and adults. (Threshold t = 3.13; $p < 10^{-3}$ and at least $p < 0.05$, FDR-corrected in 25 contiguous voxels).

2.3.2.4 Association of consistency (AUC) with brain activity during intertemporal decision making (Q4)

The regression analysis to test the association of consistency (AUC) and intertemporal decision making was restricted to the areas which were found for the main effect of intertemporal decision making. The rank-transformed consistency (AUC) was positively associated with BOLD response in left and right parietal cortex, left and right DLPFC and left and right Thalamus (Figure 2-3c,

Table 2-2).

2.4 Discussion

The main finding of our study is that neural processing of the value of delayed rewards does not differ between adolescents and adults when controlling for temporal discounting behaviour. Nevertheless, as reported previously (Green et al., 1994; Green et al., 1999) adolescents in our study also discount delayed rewards more steeply than adults, and, independent of age steeper temporal discounting is related to a lower brain response to delayed rewards. We found the most substantial difference in brain activity between adolescents and adults during intertemporal decision making when adolescents exhibited less brain activity in the parietal network and showed a lower consistency of choices than adults.

The first question, we wanted to answer was whether adolescents and adults differ in processing the value of rewards during intertemporal choice. We tried to approach this question specifically with delayed monetary rewards which were adapted subject-wise to individual discounting behaviour. We found that in adolescents and adults activity in similar brain regions represented the subjective values of delayed monetary rewards. These regions were namely the ventral striatum, the medial prefrontal cortex and the posterior cingulate gyrus which had previously been shown to process the subjective value of a reward in adults (Kable

& Glimcher, 2007; Peters & Buchel, 2009). Adolescents' brain regions processing reward value were neither hyper- nor hyposensitive compared to adults'. The adaptation of the monetary rewards to subjective impulsivity (*k*) led to the same reward levels for all subjects and to mean and variance of subjective value for each subject. Furthermore, this approach ensured that in 50% of trials, subjects of both groups chose the delayed reward. In our opinion, the distribution of decisions indicates that we successfully estimated the individual discount rate and adapted the monetary rewards to it.

In contrast, to our finding that VS, mPFC and posterior cingulate gyrus were associated with subjective values of delayed rewards McClure *et al.* (2004) showed that the activation in those areas corresponded to decisions where an immediate option was available. One possible reason for that finding as suggested for example by Monterosso and Luo (2010) and Kable and Glimcher (2007) might be that the value of rewards was higher in those trials. This led to higher activation in brain areas which are related to value processing.

Our second question was whether there is an association between discounting behaviour and neural processing of the value of monetary rewards. The adaptation procedure in our experiment led to the presentation of objectively larger amounts to more impulsive subjects. Because they discounted delayed rewards more steeply, we presented them with higher monetary rewards so that they would choose the larger later alternative at the same rate as less impulsive subjects. The relation between impulsivity and objective reward magnitude points to hyposensitivity of reward processing brain areas in more impulsive subject in the case of delayed rewards. To test this more formally, we eliminated the effect of subjective impulsivity (*k*) from the reward value by modelling data of all subjects with a fixed (i.e. median *k*) impulsivity parameter. So, we assumed the same level of discounting for each subject while computing the value of reward for each trial. This model revealed that BOLD in the ventral striatum related to reward value was inversely correlated with discounting behaviour. Therefore our

results show that processing of reward value is more related to the individual discount rate than to maturation of reward value processing areas in the brain.

In the context of other results in the domain of reward processing, the diverging developmental results (i.e. hyposensitivity vs. hypersensitivity in the reward processing areas of the brain) can be explained by hypothesising a differential role of impulsivity regarding it's relation to different tasks. The intertemporal choice task used in our study is characterised by a deterministic payoff, in a way that subjects were aware which response led to a certain reward. Since higher discounting in our study was associated with lower brain response in reward processing brain areas and the adolescents in our sample discounted delayed rewards more steeply, this study provides an explanation why the adolescent brain compared to the adults' brain seems to be hyposensitive while anticipating deterministic rewards (Bjork et al., 2004b; Bjork et al., 2010). Regarding tasks with a stochastic payoff we can only speculate: As postulated in the introduction more impulsive subjects might show hypersensitivity in reward processing areas of the brain (Hariri et al., 2006; Holt et al., 2003). This would be an explanation why the adolescent brain was hypersensitive in response to rewards in tasks with stochastic payoff (Ernst et al., 2005; Galvan et al., 2006; Van Leijenhorst et al., 2010). The next step would be, to test this hypothesis directly by comparing adolescents and adults using an individually adapted task with a stochastic payoff scheme.

However, there are exceptions which indicate that not only the task but also the measure of impulsivity might influence the relation between impulsivity and sensitivity of the reward system. Buckholtz *et al.* (2010) and Bjork *et al.*, (2012) showed hypersensitivity in a task with deterministic payoff. They used a questionnaire to measure aspects of impulsivity (i.e. psychopathic personality inventory (PPI)). Another exception is a study (Galvan et al., 2007) reporting no association between impulsivity and VS activity. The impulsivity was measured using another self-report rating of impulsivity (i.e. Connors Impulsivity Scale). It

has been shown, that self-report ratings and behavioural measurements of impulsivity are not necessarily correlated (Reynolds et al., 2006). This fact emphasises the domain-specific influence of impulsivity. The whole story seems to be more complicated when considering different measures and aspects of impulsivity.

Nevertheless, the debate about the sensitivity of the reward system has to be continued but would make progress if future studies consider the relation between tasks and discounting behaviour. Future studies should bear in mind that impulsivity measured by intertemporal choice tasks might have a differential influence on reward processing and therefore carefully select tasks or adapt them to impulsivity. This is especially crucial for studies comparing groups which differ in impulsivity (e.g. adolescents vs. adults).

The second developmental aspect we investigated with intertemporal decision making is the decision making process (Q3), which is more related to the comparison of both rewards. We found lower brain activity during decision making in adolescents compared to adults in superior and inferior parietal areas (BA7 and BA40). These regions were also reported by several studies (Boettiger et al., 2007; McClure et al., 2004; Monterosso et al., 2007) playing a role in intertemporal decision making independently of the reward value. The lower BOLD response in adolescents during intertemporal choices in the parietal decision network might be due to not yet completed maturation of these brain areas. Additionally, adults were behaviourally more consistent in their choices. One could therefore speculate that due to the already matured parietal decision network the comparison of both rewards was more precise in adults compared to adolescents. However, the effect size regarding the consistency of choices was at a moderate level (Cohen`s d = 0.41). Therefore it might be difficult to replicate these findings with small sample sizes.

Testing the association between consistency of choices and BOLD response during the decision making phase (Q4) revealed that brain responses in the same parietal areas, as well

as in the DLPFC (i.e. fronto-parietal decision network) and the thalamus were positively correlated with the behavioural consistency of choices. Whereas in our data the BOLD response in these areas was associated with more consistent decisions, McClure *et al*., (2004) reported an association with more self-controlled and patient decisions. A further contribution to more consistent decisions might be related to higher effort in mental arithmetic calculations, since it was shown that those calculations are associated to neural activation in the parietal cortex (Dehaene, Spelke, Pinel, Stanescu, & Tsivkin, 1999; Dehaene, Piazza, Pinel, & Cohen, 2003). The substantial thalamic activation in more consistent subjects may reflect more attention while doing the task (Fan, McCandliss, Fossella, Flombaum, & Posner, 2005), which might also contribute to more consistent decisions.

Inconsistent decisions might be also related to a speed-accuracy trade-off. Accuracy here refers to consistent decisions over the timecourse of the whole experiment. However, analysing the reaction times revealed no differences between adults and adolescents as well as no association between the reaction times and consistency of choices. This indicates that there was no speed-accuracy trade-off in the less consistent subjects. It is noteworthy that the subjects' consistency was not correlated with their discounting behaviour and hence it provides additional information about the subjects' behaviour during the task.

One limitation of our study that affects all developmental fMRI studies is the fact that adults and adolescents differ in the morphology and hemodynamics of the brain. Former studies have shown that children, adolescents and adults differ in perfusion measured by ASL (Biagi et al., 2007) and resting state activity measured by fMRI (Thomason, Burrows, Gabrieli, & Glover, 2005). On the other hand, in a more recent review Stevens *et al*. (2009) argued that most changes occur in the period from childhood to adolescents. This fact makes it difficult to compare children with either adolescents or adults but is not as problematic for comparisons between adolescents and adults. Another limitation is the fact that we measured im-

pulsivity only behaviourally via intertemporal choice. Since impulsivity as a personality trait is not fully represented by this means, additional studies are needed to further investigate reward processing in the brain and its relations to different aspects of impulsivity.

In summary, our study indicates that processing of delayed reward value does not differ between adolescents and adults when reward value is adapted individually to subjective impulsivity. At the same time, our data show that hyposensitivity in the ventral striatum is associated with higher impulsivity independent of age. Therefore, differences in brain reward processing are better accounted for by individual differences in temporal discounting than by age. While comparing two reward options, adolescents make less consistent choices and show lower BOLD responses in the parietal cortex (i.e. superior and inferior parietal cortex) during the decision phase. Since more activation in the fronto-parietal network is also related to higher consistency of decisions on the behavioural level, maturation of this network seems necessary for more consistent decision making.

3 Study 2: Neural Correlates of Intelligence during Inter-temporal Choices in Adolescents

3.1 Introduction

Evidence from behavioural studies has shown that temporal discounting (i.e., the propensity to devaluate future rewards), which is also commonly considered as an indicator of behavioural impulsivity (Ainslie, 1975; Reynolds et al., 2006), is negatively related to intelligence in adults (Shamosh et al., 2008; de Wit et al., 2007) and in adolescents (Freeney & O'Connell, 2010). These findings were further supported by the results of a meta-analysis showing a small to moderate inverse correlation (mean effect size r= -.234) between the rate of temporal discounting and intelligence (Shamosh & Gray, 2008). In a first attempt to reveal common neural processes underlying intelligence and temporal discounting, Shamosh *et al.*, (2008) showed that the correlation between behavioural measures of intelligence and lower temporal discounting rate was partly mediated by higher brain activation in the anterior prefrontal cortex (PFC) during a working memory (WM) task. The proposed role of WM in manipulating and integrating diverse information in order to choose between reward alternatives (Shamosh et al., 2008) is a plausible mechanism for the relation between working memory-related BOLD response in PFC and temporal discounting. However, to the best of our knowledge no study has yet directly tested whether intelligence is related to activity in WM-associated brain circuitry during an intertemporal choice task. Investigations of such relations will shed new light on potential overlaps between brain circuitries implicating temporal discounting and intelligence.

Steeper rates of discounting delayed rewards, which are associated with proclivity for immediate rewards, have been considered as an important component in the development and

persistence of addictive behaviour (Bickel et al., 2007). For example, it has been shown that more extreme discounting is related to excessive substance use (Bickel et al., 1999; Reynolds et al., 2007) and gambling (Holt et al., 2003). The integrity of brain circuitry underlying the inverse relation between intelligence and temporal discounting might, thus be a protective factor against the development of addictive behaviour, such as substance abuse (Sjolund, Allebeck, & Hemmingsson, 2012). This is of particular relevance for adolescent development: given the maturational gap of the prefrontal circuitry lagging behind the development of subcortical circuitry (Casey, Tottenham, Liston, & Durston, 2005; Casey, Jones, & Hare, 2008; Steinberg, 2005), adolescence may be a period when the yet-to-mature prefrontal regulatory functions are vulnerable to subcortical circuitry's heightened sensitivity to environmental stimuli, such as alcohol, illicit drug, or risky activities, that elicit high motivational or affective valences (Crone & Dahl, 2012).

3.1.1 Brain networks of intertemporal choice

Decision research on intertemporal choices, i.e. choosing between a small immediate reward and a larger but delayed reward, suggests that making such decisions consists of two processes that may both be related to intelligence. Specifically, at one level there is the decision process of comparing between alternative options independent of either the subjective values of the options or the actual choices (Hoffman et al., 2008; McClure et al., 2004; Monterosso et al., 2007). Activity in frontal brain regions, such as the ventrolateral and dorsolateral prefrontal cortex (VLPFC and DLPFC), the anterior cingulate cortex (ACC) as well as parietal brain regions, like the intra-parietal sulcus (IPS) and the posterior parietal cortex (PPC) have been shown to implicate decision making. At the other level, there is the valuation process that evaluates the subjective values of the choice options and is sensitive to the temporal features of the choice outcomes (Kable & Glimcher, 2007; Peters & Buchel, 2009). The

blood-oxygen-level-dependent response (BOLD response) in brain regions, such as the ventral striatum (VS), medial prefrontal cortex (MPFC) and posterior cingulate cortex (PCC) have been found to implicate representations of the subjective values of delayed rewards (Kable & Glimcher, 2007). In addition, frontal regions, such as the anterior cingulate cortex (ACC) and the inferior frontal gyrus (IFG), have also been found to be associated with value processing (Kable & Glimcher, 2007; Ripke et al., 2012).

Focusing more specifically on the rate of temporal discounting, it has been shown in adults that steeper discounting was related to hypoactivity of the VS while processing the value of delayed rewards (Ballard & Knutson, 2009). Recently, we found the same association in adolescents as well as in adults. Moreover, neither in subcortical nor in cortical brain areas did we find a difference between adolescents and adults regarding value processing during intertemporal choices (Ripke et al., 2012). Thus, value processing during adolescence and young adulthood might be more sensitive to other individual difference factors, such as intelligence and the relevant brain circuitry, than chronological age. Cortical brain regions involved in value processing, such as the IFG and the ACC, might be associated with less impulsive decisions. For example the IFG as part of the prefrontal cortex has been shown to be a region which is associated to the inhibition of prepotent responses (cf. Aron, Robbins, & Poldrack, 2004). Moreover, it has been proposed that the IFG inhibits the prepotent immediate choice during intertemporal decisions in order to thoroughly evaluate difference choice alternatives (Ballard & Knutson, 2009). Relatedly, it has been shown to be more activated during decisions for the delayed reward (Luo et al., 2012) and in individuals who discounted less steeply (Liu, Feng, Wang, & Li, 2012).

Besides the discounting rate, the consistency of choices is a second behavioural measure of intertemporal choice that is less examined. Generally, consistency is a behavioural parameter which describes the balance between exploration and exploitation in different tasks,

such as in reinforcement learning (Suton & Barto, 1998). Consistency in intertemporal choice refers to the degree to which subjects choose the alternative with the higher subjective value over the time course of the task and has been shown to be related to higher BOLD in a fronto-parietal brain network during intertemporal choices (Ripke et al., 2012).

3.1.2 Components of intelligence

Since Spearman (1904) identified the positive manifold of measures of intelligence more than a century ago (see a contemporary review in Lubinski, 2004), the multiple sub-facets of intelligence have been subjected to intensive research. At a high-level of abstraction, the commonly subscribed two-factor theory categorises intelligence into two broad sub-components, i.e. crystallised and fluid intelligence (Cattell, 1943; Cattell, 1963; Horn & Cattell, 1966; Horn, 1968; see Nisbett et al., 2012 for review). Categorised as such, crystallised intelligence refers to cognitive pragmatics and acquired knowledge that are relatively more experience- and culture-dependent, whereas fluid intelligence refers to the cognitive mechanics of information processing, reasoning, and abstract thinking that are relatively more neurobiology-based (cf. Baltes, 1987; Horn & Cattell, 1966; Li et al., 2004). Crystallised intelligence is often measured by tasks of verbal knowledge and fluid intelligence is usually assessed by reasoning and problem solving tasks as well as other measures of basic information processing, such as perceptual speed and memory ability. So far, correlations between temporal discounting rates and intelligence have been found with crystallised intelligence (Olson, Hooper, Collins, & Luciana, 2007), as well as the full scale of general intelligence including both crystallised and fluid intelligence (de Wit et al., 2007; Shamosh et al., 2008).

3.1.3 Neural correlates of intelligence and their relation to intertemporal choices

Neural correlates of intelligence have been widely investigated. The parieto-frontal integration theory (P-FIT; Jung & Haier, 2007) suggests that a network consisting of the inferior

(BA 39, 40) and superior parietal lobes (BA 7) interact with frontal regions (i.e., DLPFC, BA 6, 9, 10, 45, 46, 47) to serve processes of comparing various solutions during reasoning and problem solving. The anterior cingulate cortex (BA 32) then engages in selectively facilitating the selected responses and inhibiting non-selected ones. Regions within the temporal (BA 21, 37) and occipital (BA 18, 19) lobes process visual and auditory inputs. This theory was further supported by studies (Colom et al., 2009; Johnson et al., 2008; Karama et al., 2009) showing that higher scores in fluid and crystallised intelligence were related to higher grey matter volume in these areas. Recently, a higher cortical thickness of the superior frontal cortex has been proposed as common neural basis of intelligence and impulsivity (Schilling et al., 2012). Some studies also show common functional activation patterns (lateral frontal brain areas and parietal brain areas) in tasks where performance is highly correlated with Spearman's *g* (e.g., problem solving or WM), using positron emission tomography (Duncan et al., 2000) or functional magnetic resonance imaging (fMRI; Waiter et al., 2009). Experimentally, although tasks where performance is correlated with *g* seem to require more activation especially in frontal and parietal brain areas, the patterns of associations between individual differences in intelligence and BOLD responses in these regions are less clear. On the one hand, some fMRI studies have shown that subjects who scored higher on intelligence measures recruited less neural resources (i.e. lower BOLD response during the task) during visuo-spatial (Haier et al., 1992) or n-back WM tasks (Tang et al., 2010), which is described as neural efficiency. On the other hand, other studies showed that individuals who scored higher on intelligence measures recruited more neural resources during complex reasoning (Lee et al., 2006) and set shifting (Graham et al., 2010). These BOLD differences between high and low intelligent subjects were interpreted as functional facilitation (Lee et al., 2006) and may reflect strategy differences between individuals (Graham et al., 2010). The conflicting findings may not be necessarily mutually exclusive. For instance, it has been proposed that an increase in

neural activity in high intelligence individuals manifests especially under conditions with higher task difficulty (Gray et al., 2003) or more restrictions (Lamm et al., 2001) and the higher brain activities usually are accompanied by better performance. Together these findings suggest that, with load task demands more intelligent individuals recruit less brain resources to performance at the same level as individuals low on intellectual abilities; with high task demands, more intelligent individuals were able to recruit additional brain resources and could reach higher level of performance than individuals scored lower on intelligence measures.

In summary, brain networks (i.e. VLPFC, DLPFC, ACC, IPS and PPC) shown to be functionally associated to intelligence have also been shown to be involved in intertemporal choices (McClure et al., 2004; Hoffman et al., 2008; Monterosso et al., 2007). This may not be surprising, since information integration is required to decide between choice alternatives. Moreover, higher BOLD in these regions has been shown to be related to higher consistency of choices in an intertemporal choice task (Ripke et al., 2012). Thus, it is very likely that the relation between intelligence and behavioural measures of intertemporal choices arise from the decision and valuation processes of intertemporal choice, which, in part, share overlapping brain networks with intelligence. However, to date no study has yet directly tested whether individual differences in intelligence are related to BOLD responses in WM-associated brain circuitry during an intertemporal choice task.

3.1.4 Study aims and hypotheses

The aim of the current study was to explore the neural basis for the association between intelligence and the behavioural measures of intertemporal choice tasks, which have been reported in a handful a recent studies (see review in the introduction above). Specifically, we tested the conjecture about potential overlaps in the brain circuitries underlying intelli-

gence and delayed discounting during intertemporal choices. We hypothesized that BOLD responses in brain regions implicating decision processing or valuation would be associated with temporal discounting behaviour and individual differences in intelligence. In addition to expecting a negative correlation between the temporal discounting rate and intelligence as reported in previous behavioural studies (see meta-analysis Shamosh et al., 2008), we further expected more intelligent individuals to be more consistent in their decisions.

According to the P-FIT (Jung & Haier, 2007), we hypothesised that neural correlates of relevant for decision processes involved in intertemporal decision making would be related to intelligence. According to previous results showing higher BOLD response to be related to better performance, we expected higher level of BOLD to be associated with higher choice consistency during the task.

As to the processing of reward value, we expected BOLD differences in subcortical brain areas (i.e. the VS) where brain activity has been shown to be inversely related to the discount rate be associated with intelligence. Furthermore, we also hypothesised BOLD differences in cortical brain regions among the reward value processing brain areas, which have been formerly shown to inhibit prepotent responses (i.e. IFG). If differences in the discounting rate which are related to intelligence would rely on BOLD differences during value processing in these brain regions, BOLD response in turn should be related to discount rates. As regarding choice consistency, we hypothesized that a higher level of consistency in more intelligent individuals may be achieved by recruiting a higher amount of neural resources (i.e. level of BOLD response) during the intertemporal choices.

We investigated these hypotheses in two steps. First, we investigated whether intelligence would be related to BOLD response during the decision making phase and the reward valuation phase of intertemporal choice. Second, we tested whether the behavioural measures of intertemporal choice (i.e. consistency of choices and discounting rate) would be related to

BOLD response in the brain areas identified to be associated with individual differences in intelligence.

3.2 Method

3.2.1 Subjects

The acquisition of data was part of the project "The adolescent brain", which is funded by the German Federal Ministry of Education and Research (BMBF). The project aims to investigate structural and functional brain development in the context of environmental and genetic factors from a longitudinal perspective and is related to the IMAGEN project, funded by the European Commission (for more details regarding the projects see Ripke et al., 2012 and; Schumann et al., 2010).

260 adolescent subjects and one of their legal guardians signed informed consent and were invited to take part in the study. They received monetary compensation for their participation. 235 of them (122 males, mean age: 14.6, SD = 0.3, min: 13.7, max: 15.5) participated in the two parts of the intertemporal choice task (training session and imaging session). They received additional monetary compensation depending on their decisions during the task. The compensation for the task ranged from 5 to 35 Euro.

All subjects with mental disorders, including substance use disorder were excluded from the sample according the Development and Well-Being Assessment (DAWBA, Goodman et al., 2000), which is a well validated questionnaire for children and adolescents from age 5 to 17. All participants had normal or corrected to normal vision. Seven of the adolescent datasets were incomplete due to technical difficulties during the imaging session and the data of 10 further adolescents were excluded due to signal drop out. For further 8 participants there were no IQ data available. After these exclusions, the final data analysis included 210 subjects.

3.2.2 Intertemporal choice task

The intertemporal choice task used in our study consisted of two sessions. First, a training session was performed outside the MRI scanner that served to estimate individual discount rate as well as to train the participant for the subsequent imaging session. In order to give the participants time to understand the task and response procedure, the first 3 trials in the training session were not included in the behavioural analysis. After these three trials, each participant underwent 50 behavioural decision trials. In each of the trials subjects had to choose either a small immediate amount of money or a larger amount of money paid after a delay. Before the task started, we instructed the participants that the immediate amount would be 20 Euros in every trial. At the beginning of each trial, subjects saw the amount and delay of money being delivered later. After 2 seconds, subjects had to indicate their preference by pressing either the left button (for the later alternative) or the right button (for the immediate option). Directly after their response, subjects received feedback on the amount and delay chosen (either of the immediate or later reward) to ensure that participants could monitor their decisions. For each of the five delays (10, 30, 60, 120 or 180 days), subjects had to make 10 decisions. After 10 trials, the delay changed for the next 10 decisions. The training session was adaptive, i.e. the amounts of money displayed increased or decreased based on the subject's decision in the previous trial. For instance, if the immediate amount was chosen, for the next trial the delayed amount increased by 50% of the difference between immediate and delayed rewards and vice versa. Based on the choices in these 50 trials, we estimated the individual discount parameter *k*. First, we estimated the indifference amount for each of the five delays, i.e. the mean of the maximum delayed amount rejected and the minimum delayed amount chosen. The indifference amount represents the quantity (*A*) in the hyperbolic function:

$$V = \frac{A}{1 + k \times D}.$$

Further, in this equation *V* represents the subjective value of a reward (during our training session it was 20 Euro), *D* the delay, and *k* the individual discount parameter. Using ordinary least square estimation, Parameter *k* was estimated to best fit the hyperbolic curve consisting of 6 points, i.e. 20 Euros for a delay of 0 (immediate reward) and the indifference amounts of the 5 delays. We used a hyperbolic function, because previous studies found that it best fits the data (Simpson & Vuchinich, 2000; Mazur, 1987; Kirby & Marakovic, 1995).

We adapted the intertemporal choices presented during the imaging session of the task to the individual level of impulsivity (*k*) in a way that (1) subjects ought to choose the immediate reward in 50% of trials, according to the procedure of Kable & Glimcher (2007) (2) the mean value (*V*) of all delayed rewards would be the same (30 Euro) for each subject, and (3) the maximal value (*V*) of all rewards was twentyfold the minimum value. For further information regarding the adaptation see Ripke *et al.*, (2012).

Pairs of amounts and delays were computed in advance and presented in random order during the imaging session of the experiment. The immediate amount was also adapted for each participant so that rewards were presented with the same mean value over all trials for each subject. So the immediate reward differed from the 20 Euro during the training session, but was the same in all trials. The delayed larger amount and the respective delay were presented for 2 seconds (Figure 3). After a further period of 6 seconds during which a fixation cross was displayed, the response timeframe (2 seconds) started. An exclamation mark on the left or right side of the screen indicated to the participant which button was mapped onto the larger delayed amount. In order to avoid lateralization effects of response, in fifty percent of the trials the decision for the delayed reward was mapped to the right button and in fifty percent of the trials to the left one. Each trial of the experiment ended with feedback of the par-

ticipants' decision (amount and delay was shown) followed by an inter-trial-interval (ITI) with a duration of seven seconds on average (uniform distribution). The whole session (90 trials) lasted 25 minutes.

The participants were told that one of their choices was selected by chance and paid exactly in 10, 30, 60, 120 or 180 days via bank transfer or immediately after scanning. We integrated this procedure to ensure that participants made realistic choices and to increase task relevance (Zink et al., 2004).

3.2.3 Intelligence measure

For assessing intelligence we administered 4 subtests of the German version of the Wechsler intelligence scale for children and adolescents (Hamburg Wechsler Intelligenztest für Kinder (HAWIK), Daseking et al., 2007). The subtests included vocabulary, similarities, block design and matrix reasoning. For the analysis in the current study, the verbal comprehension index was estimated from the subtests of vocabulary and similarities, whereas the perceptual reasoning index was estimated from the subtests of block design and matrices. Verbal comprehension is a commonly used indicator of crystallised intelligence (*gc*) or the so-called cognitive pragamtics, whereas perceptual reasoning is an indicator of fluid intelligence (*gf*) or the so-called cognitive mechanics (Baltes, 1987; Li et al., 2004).

3.2.4 fMRI data acquisition

Scanning was performed with a 3 T whole-body MR tomograph (Magnetom TRIO, Siemens, Erlangen, Germany) equipped with a standard head coil. For functional imaging, a standard Echo Planar Imaging (EPI) Sequence was used (repetition time (TR): 2410 ms; echo time (TE): 25 ms; flip angle: 80°). fMRI scans were obtained from 42 transversal slices, orientated 30° clockwise to the anterior commissure–posterior commissure line, with a thickness of 2 mm (1 mm gap), a field of view (FOV) of 192 x 192 mm and an in-plane resolution of 64

x 64 pixels, resulting in a voxel size of 3 x 3 x 3 mm. To exclude structural abnormalities, a 3D T1-weighted magnetization-prepared rapid gradient echo (MPRAGE) image data set was acquired (TR = 1900 ms, TE = 2.26 ms, FOV = 256 x 256 mm, 176 slices, 1 x 1 x 1 mm^3 voxel size, flip angle = 9°). Images were presented via NNL goggles (Nordic Neurolab, Bergen, Norway). Task presentation and recording of the behavioural responses was performed using Presentation® software (version 11.1, Neurobehavioral Systems, Inc., Albany, CA).

3.2.5 Behavioural data analysis

We estimated two different behavioural parameters, the discount parameter *k* and the consistency of choices. Consistency of choices here denotes the degree to which subjects consistently chose the alternative with the higher subjective value. To compute the consistency parameter we ran a Receiver Operating Characteristics (ROC) curve analysis with subjective values of the delayed reward as a predictor for the respective choice. For each subject, we computed the area under the curve (*AUC*) from the data of the scanning session, which was supposed to be higher for more consistent subjects (i.e. always choosing the reward with the higher value results in an *AUC* of 1; complete randomness of choices would yield an *AUC* of 0.5). Statistical testing and determination of *AUC* was computed with SPSS 19.

The discounting parameter *k* was computed using the fitting procedure described for data of the training session, which was applied to the data of the imaging session using MATLAB 7.1.

Because *AUC* and *k* were not normally distributed we analysed the associations between both behavioural measures and both intelligence measures (*gc* and *gf*) using non-parametric statistical testing. The significance level for all statistical testing was set at $\alpha = 5\%$ (two-tailed).

Due to the fact that *gc* has been shown to be related to education level (Cliffordson & Gustafsson, 2008; Ceci, 1991), we tested whether environmental factors which affect education, i.e. participants' socio-demographics might be associated with intelligence and behavioural measures of intertemporal choice. Specifically, we analysed the association between parents' educational attainment, *gc*, discounting rate *k* and consistency of choices (*AUC*).

3.2.6 MRI data analysis

We analysed functional MRI data using statistical parametric mapping (SPM 5, Wellcome Department of Neuroimaging, London, United Kingdom). For preprocessing, data were corrected for temporal differences in scantime to minimize temporal differences in slice acquisition and inter-scan head motions over course of the session. The scans were then normalized to the standard EPI template (MNI) and finally smoothed using an isotropic Gaussian kernel (8 mm full-width at half-maximum).

Our first level model consisted of four regressors for different events and one parameter. The decision making phase (presentation of the delayed reward) was the first regressor, which was parametrically modulated by the value of the delayed reward. The reward value was computed based on a fixed *k* (fixed k=0.01). The fixed *k* was chosen to preserve differences in reward processing related to subjective discounting.

The subsequent motor response/feedback (separated for responses with the left and right hand) were modelled as second and third regressor. Trials with implausible decisions based on analysis of the behavioural data from the imaging session (i.e. trials with a decision for a reward with a subjective value lower than half of the alternative reward) and trials without response (missing trial) were regarded as invalid. This was done to make sure that only trials in which subjects decided properly were included into the analysis. The presentation of the delayed reward of invalid trials was modelled as the fourth regressor. For trials with im-

plausible choices, the subsequent motor response was modelled using the same regressor as in valid trials. All events were modelled using the canonical hemodynamic response function (HRF). To alleviate the effects of subjects' movement, we integrated the six realignment parameters (three translation and three rotation parameters) as regressors of no interest.

For the second level analysis we built up two regression models with two covariates: *gc*, *gf*, and BOLD response during decision making (model 1) and reward value related BOLD (model 2) as dependent variable. This was done to identify brain networks, where the BOLD response was related to either *gc* or *gf*. As we hypothesised that individual differences in intelligence, if associated with behaviour during intertemporal choice, would be mediated through brain networks relevant for intertemporal choice, our regression analyses focused on regions that showed main effects of BOLD responses with respect to decision making and value processing. For details of the mask of our regions of interest see supplementary Figure 1 (a: for decision process and b: for value processing). All reported results regarding the regressions reached corrected threshold of $p<0.05$, FDR-corrected in at least 25 contiguous voxels.

To analyse whether the BOLD responses within the networks, which were identified by the regression analyses, would be in turn also associated to the consistency of behavioural choices (*AUC*) and temporal discounting rate (*k*), we correlated the BOLD signal changes in ROIs that were extracted from the respective networks of the decision and the value processing phases with both behavioural parameters. These functional ROIs were binary masks of the respective activation map (see results section). For the correlation analyses significance level was set at $\alpha = 5\%$ (two-tailed).

Since we also hypothesised that intelligence and the behavioural measures have a common neural correlate we tested whether the correlations between *gc*, *k* and the *AUC* are mediated by the BOLD in the respective ROI (i.e. BA7 and IFG). Therefore, we also ran a post-hoc partial correlation analysis.

3.3 Results

3.3.1 Behavioural results

The mean of the *gc* was 112.55 (SD = 12.68, range = 77 - 140) and the mean of *gf* was 113.15 (SD = 12.27, range = 75 - 147). *gc* and *gf* were positively correlated with each other ($r = 0.445$, $p < 0.001$) as to be expected from the positive manifold of intelligence (Spearmann, 1904). The median of *k* was $Md_k = 0.029$ with an interquartile range of $IQR_k = 0.0388$ and the median of the *AUC* was $Md_{AUC} = 0.963$ with an interquartile range of $IQR_{AUC} = 0.0710$. The discount rate *k* and *AUC* were not correlated ($r = -0.051$, $p = 0.463$). As expected, *k* was negatively correlated with intelligence (*gc*: $r = -.188$, $p < 0.007$; *gf*: $r = -0.191$, $p < 0.006$), whereas the *AUC* was positively correlated with intelligence (*gc*: $r = 0.161$, $p < 0.019$; *gf*: $r = 0.173$, $p < 0.012$).

The correlational analysis of the associations between parents' educational attainment, *gc*, *k* and *AUC* revealed positive correlations between *gc* and mother's ($r = 0.450$, $p < 0.001$) as well as father's ($r = 0.441$, $p < 0.001$) educational attainment. Correlations between *gf* and the parental education were significant but weaker (mother: $r = 0.214$, $p = 0.002$; father: $r = 0.269$, $p < 0.001$). The temporal discount rate (*k*) was negatively correlated with mother's ($r = -0.242$, $p < 0.001$) and father's ($r = -0.169$, $p = 0.016$) educational attainment, whereas consistency of choices (*AUC*) was not correlated to parents' education.

3.3.2 Imaging results

3.3.2.1 Neural correlates of intelligence during the decision phase of intertemporal choices

The regression analyses to test whether BOLD responses in the decision network were related to either *gc* or *gf* revealed positive correlations between *gc* and the BOLD response in

the parietal cortex (precuneus/ BA7) as well as in the dorsolateral prefrontal cortex (DLPFC/ BA9) and the occipital lobe (BAs 18, 19, 31). The areas in the parietal lobe (BA7) and the frontal lobe (BA9) were used as functional ROIs for further correlational analyses (Figure 1a, middle).

There were no significant correlations between BOLD response during the decision phase and *gf*.

3.3.2.2 Neural correlates of intelligence during value processing

The regression analysis revealed a frontal network consisting of the anterior cingulate cortex (ACC) and the inferior frontal gyrus (IFG) where higher BOLD was related to higher *gc*. Both areas were used during the further analyses as functional ROIs (Figure 3-1b, middle). There was no significant association between brain activity during value processing and *gf*.

3.3.2.3 Correlations between behavioural intertemporal choice measures and BOLD response in functional ROIs related to crystallised intelligence

The correlations between the behavioural outcome measures of intertemporal choices and BOLD response were tested in different functional ROIs. These ROIs were exactly the regions where BOLD response was related to crystallised intelligence (*gc*). For the decision making phase these regions were the precuneus and the inferior parietal cortex (BA7) as one ROI and the DLPFC (BA9) as the second one. Functional ROIs regarding the processing of reward value included the ACC as one ROI and the IFG as the second ROI.

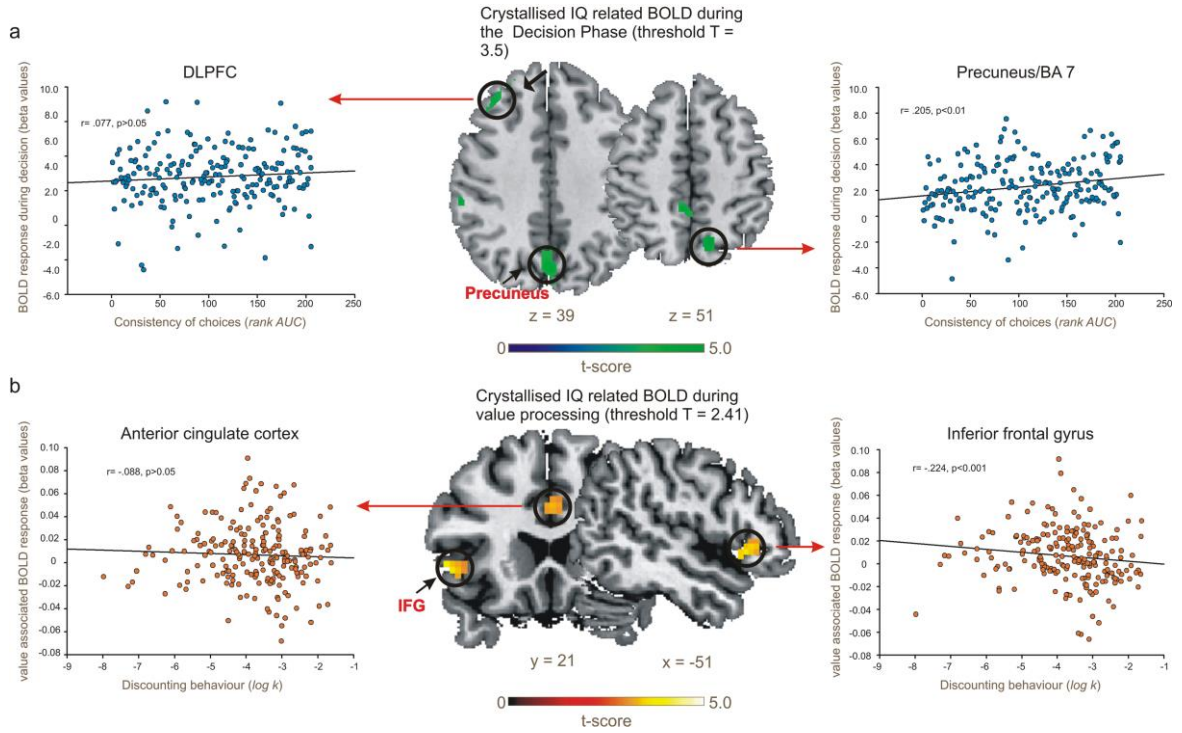

Figure 3-1:Intelligence related BOLD in adolescents: a (middle): Crystallised intelligence related BOLD response during decision phase (Threshold t = 3.5, p<0.05, FDR corrected). a (right): The BOLD signal change was positively correlated to the consistency of choices (rank AUC) during the decision in the precuneus and BA7 ROI. a (left): There was no correlation in the DLPFC. b (middle): Crystallised intelligence related BOLD response during reward value processing (Threshold t = 2.41, p<0.05, FDR corrected). b (right): The BOLD signal change in the IFG, which was related to the processing of delayed rewards was negatively correlated to the discount rate (log k). b (left): There was no correlation in the ACC.

The analysis revealed that consistency of choices (*AUC*) was positively correlated with BOLD in the parietal part of the decision network during decisions (Figure 3-1a, right). There was no association between *k* and the BOLD response during the decision epoch related ROIs (Table 3-1).

Reward value related BOLD in the IFG was inversely correlated to *k* (Figure 3-1b, right). There was no association between BOLD in the IFG and the consistency of choices and no association between BOLD in the ACC and any of the behavioural measures (Table 3-2).

Table 3-1: Brain behaviour correlations for functional ROI analysis: Associations between behavioural measures during the intertemporal choice task and decision phase related BOLD response in brain areas where BOLD was higher in more intelligent (gc) subjects.

ROI	Peak coordinates			*T* max.	Behavioural measure	Non-parametric correlations
	x	Y	Z			
Parietal cortex, Precuneus, BA7	12	-66	51	5.21	Discount rate *k*	r = -.048 (p>0.489)
					Consistency *AUC*	r = **.205 (p<0.003)**
Dorsolateral prefrontal cortex (DLPFC), BA9	-39	36	39	4.07	Discount rate *k*	r = -.060 (p>0.265)
					Consistency *AUC*	r = .077 (p>0.393)

Table 3-2: Brain behaviour correlations for functional ROI analysis: Associations between behavioural measures during the intertemporal choice task and reward value related BOLD response in brain areas where BOLD was higher in more intelligent (gc) subjects.

ROI	Peak coordinates			*T* max.	Behavioural measure	Non-parametric correlations
	x	Y	Z			
Anterior cingulate cortex (ACC), BA32	0	21	33	3.35	Discount rate *k*	r = -.088 (p=0.204)
					Consistency *AUC*	r = -.025 (p=0.719)
Inferior frontal gyrus (IFG)	-45	27	0	3.78	Discount rate *k*	**r = -.224 (p=0.001)**
					Consistency *AUC*	r = -.007 (p=0.918)

After controlling (partial correlation) for the BOLD response the correlation between *gc* and consistency decreased from r = 0.161 to r = 0.086 and was no longer significant (p = 0.218). The correlation between *gc* and discounting dropped from r = -0.188 to r = -0.142, but was still significant (p=0.042). Statistical testing between zero order correlations

and partial correlations as proposed by Olkin & Finn (1995), revealed no significant differences ($z_{consistency}$ = -1.09, p = 0.138; $z_{discounting}$ = 0.67, p = 0.248).

3.4 Discussion

This study is the first showing the associations between the neural response during an intertemporal choice task and intelligence. Higher intelligence was associated with higher BOLD in a parieto-frontal network during the decision, which was positively correlated to consistency of choices. Additionally, we found that higher intelligence was related to higher activation during reward value processing in a frontal network consisting of the anterior cingulate cortex and the inferior frontal gyrus (IFG). Moreover, the BOLD response in the IFG was negatively correlated to the discount rate. The post-hoc partial correlations showed that correlations between behaviour and intelligence decreased after controlling for BOLD in the respective ROI. This indicates that the associations between intelligence and temporal discounting or consistency of choices are partly mediated by BOLD response in the respective brain network.

The positive correlation between BOLD response in the parietal cortex and the frontal cortex and crystallised intelligence during the decision making is consistent with studies which found more brain activity in those areas during working memory or reasoning tasks (Duncan et al., 2000; Waiter et al., 2009). Both, working memory and problem solving abilities, are required during decision making. For example, to make consistent decisions the evaluation algorithm has to be kept in working memory during the timecourse of the task. Indeed, in our study intelligence was also related to the consistency of choices (*AUC*). Our results show that more intelligent adolescents were more precise in their decisions. Further, the intelligence related BOLD in the parietal part (Precuneus, BA7) of the fronto-parietal network was related to behavioural consistency. Thus, the higher BOLD might be a link between higher

crystallised intelligence and more consistent decisions. To test this link, we ran an additional post-hoc partial correlation. After controlling for BOLD in the BA7, the correlations between behaviour and intelligence decreased. Thus, more intelligent subjects show higher BOLD response (i.e. they use more neural resources) for each trial during the intertemporal choice task and this might at least partly lead to more precise decisions. On the one hand our findings do not support the efficiency model (Haier et al., 1992; Tang et al., 2010), which states that more intelligent subjects require less resources (lower BOLD) compared to less intelligent subjects. But on the other hand the results do not preclude this model, because the contributions of using more resources and process decisions more efficiently might add up and lead to more consistent decisions. Our results were in line with former studies which have shown a positive relationship between intelligence and BOLD response in a parieto-frontal network, by comparing groups with high versus average intelligence (Graham et al., 2010; Lee et al., 2006). As in our study, in these studies the use of more resources was accompanied by better performance. Higher brain activity was also found in more intelligent subjects while performing more difficult tasks in an fMRI study (Gray et al., 2003) or time restricted tasks in a study measuring event-related slow cortical potentials (Lamm et al., 2001). This can be interpreted in the sense of a mental resource theory (Bunge, Klingberg, Jacobsen, & Gabrieli, 2000). This theory states that more resources are needed to perform a task better.

The second process of intertemporal choices is reward value processing (Kable & Glimcher, 2007; Peters & Buchel, 2010). Our results revealed a higher BOLD response in a frontal network (i.e. the ACC and IFG) while processing the value of delayed rewards in more intelligent adolescents. Moreover, a higher BOLD signal in the IFG was also related to a lower discounting rate. This implicates a possible neural mechanism mediating the link between intelligence and discounting. The association between higher IFG activation and lower discounting has been shown before by Liu *et al.*, (2012). This fact and the finding that higher

BOLD in the IFG is related to inhibition in general (Aron et al., 2004; Swick, Ashley, & Turken, 2011) and during intertemporal choices (Ballard & Knutson, 2009) strengthens the hypothesis that higher BOLD signal in the IFG might be one possible link between higher intelligence scores and lower discounting of delayed rewards, which was found in several behavioural studies (de Wit et al., 2007; Freeney & O'Connell, 2010; Shamosh et al., 2008; Shamosh & Gray, 2008). This was further supported by the post-hoc partial correlation controlling for BOLD in the IFG which led to a decrease in the correlation between intelligence and the discounting rate. We did not find any support for the hypothesis that less hyposensitivity in the VS might be a link between intelligence and the discount rate. This implicates that responsivity of cortical rather than of subcortical brain areas might be the link between intelligence and the discount rate.

Although fluid as well as crystallised intelligence were related to choice consistency and steeper discounting, only crystallised intelligence was correlated to the BOLD response during the decision making phase and value processing. The fact that only crystallised intelligence was associated with both processes might implicate that education is associated to behaviour during intertemporal choices as well. Higher levels of crystallised intelligence, which benefit from education, might also be related to other environmental factors, like socio-demographics. Indeed, in our data parents' educational level was positively correlated to their children's crystallised intelligence, and negatively to the discounting rate, but not to consistency of choices. This finding might implicate that education and environmental factors might affect discounting via crystallised intelligence. Further support for this line of reasoning comes from several studies which showed associations between education in school and delay discounting in different populations (Bauer & Chytilova, 2010; Harrison, Lau, & Williams, 2002; Kirby et al., 2002; Reimers, Maylor, Stewart, & Chater, 2009).

Because substance use has been shown to be related to steeper discounting (Bickel et al., 2007), one might speculate that better education at school and at home might be related to less impulsive behaviour and hence to lower risk for substance use. This implicates that studying this issue in adolescents is very important, since education (at school) has been shown to positively affect crystallised intelligence (Ceci, 1991; Ceci & Williams, 1997; van Tuijl & Lesernan, 2007). Higher crystallised intelligence might then have an impact on the discount rate. Education has also been linked directly to substance use. It has been shown that smokers with higher education discount delayed rewards less steeply than smokers with a lower level of education. It was proposed that this might play a role in cessation success (Jaroni et al., 2004). Mediated by intelligence, higher education and a supportive environment might be protecting factors, which both have an effect on the discount rate and subsequently affect substance use behaviour.

Lastly, a few caveats of our study should be discussed. First, our sample only consists of adolescents. But, as mentioned before it might be of special interest to know about associations between intelligence, temporal discounting and neural processing in adolescence. Due to the results of our former study indicating differences between adults and adolescents only for the processing of decisions, one could speculate that the intelligence differences regarding reward processing could also be found in the adult brain. Thus the proposed protective role of intelligence regarding substance use might be important later in life as well. Nevertheless studies with adults are necessary to further investigate these associations. Another limitation might be the fact that we have only an estimation of fluid and crystallised intelligence through a subset of four WISC subtests. The tests we used were based on the WASI (Wechsler Abbreviated Scale of Intelligence) and should provide a reliable estimation of intelligence (Axelrod, 2002; Hays, Reas, & Shaw, 2002; Zhu, Tulsky, & Leyva, 1999). Finally, the correlations between intelligence and the behavioural measures represent only small to moderate effects.

Actually, we did not expect much stronger effects because Shamosh *et al.* (2008) showed an effect of r = -0.234 in their meta-analysis. Thus, our results seem to be reliable. Nevertheless, all results have to be interpreted with caution, especially the results of the post-hoc partial correlations which did not differ significantly from the zero order correlations.

In conclusion, for the first time we were able to show possible neural correlates behind the associations between the discount rate, consistency of choices and intelligence. Stronger BOLD response in the parietal part of the parieto-frontal network during decision making might cause the higher consistency of choices in more intelligent adolescents. Higher BOLD response in parts of a frontal control and inhibition network in more intelligent subjects might lead to more patient behaviour. The positive association between the environmental factor of parental education level, crystallised intelligence and a lower discount rate on the one hand and the fact that the negative association between intelligence and discounting is partly due to BOLD differences in the same brain areas on the other hand, might reflect a mechanism how environmental factors influence temporal discounting. Since lower discounting rates and higher intelligence have been shown to be associated with lower rates of substance use, these findings might provide a possible neural correlate of the protecting effect of environmental factors in regard to initiation and maintenance of substance use.

4 Study 3: Acute and Chronic Nicotine Effects on Behaviour and Brain Activation during Intertemporal Decision Making

4.1 Introduction

Discounting of delayed rewards describes the degree towards preferring options with immediate payoffs over larger, but delayed ones. This facet of impulsivity is thought to contribute to developing addictive behaviour, e.g. tobacco dependence. In case of chronic cigarette smoking immediate effects which are desired by the smoker (e.g. instant dopamine release and alleviation of withdrawal symptoms) compete against desirable but distant effects of smoking abstinence (e.g. increase of physical health and fitness). Previous research demonstrated higher discounting rates for delayed rewards in (light and heavy) smokers than in 1) non-smokers (Baker et al. 2003, Johnson et al. 2007), 2) non-smokers and ex-smokers (Bickel et al. 1999), and 3) non-smokers, occasional smokers and ex-smokers whose discounting rates did not differ from one another (Bickel et al., 1999; Sweitzer et al., 2008).

These differences in smokers' intertemporal choices could have different accounts (not all of them are mutually exclusive). First, pharmacological effects of nicotine intake might induce a reversible adaptation of the neural reward circuitry which alters intertemporal decision making. Second, chronic nicotine intake might irreversibly alter the neural reward circuitry. Third, differences could be due to pre-drug group characteristics. Higher discounting in young-adult smokers compared to adolescent smokers and non-smokers has been interpreted as supporting the first cause (Reynolds, 2004). Positive correlations between the discounting rate and the number of daily cigarettes as well as the estimated dose of nicotine have furthermore been interpreted as indirect support for a dose-dependent pharmacological effect

(Ohmura et al., 2005; Reynolds, 2004). Notably, these findings could equally be interpreted as supporting the pre-drug characteristic hypothesis. Thus, moderate discounters might develop moderate cigarette consumption, while high discounters might develop high cigarette consumption. A reversible effect of nicotine is indicated by the finding of a decrease of discounting in dependent smokers who were reinforced to refrain from smoking for five days (Yi et al., 2008). Contrary to this effect of smoking reduction, shorter nicotine deprivation (13 hours) led to an increase of impulsive choices for monetary rewards (Field et al., 2006), whereas 24 hours of abstinence did not alter discounting of delayed monetary rewards (Mitchell, 2004). These diverging results could partly be due to different degrees of acute withdrawal symptoms that might additionally affect discounting behaviour. In order to avoid blending of the effects of withdrawal symptoms and nicotine abstinence, longitudinal studies are needed investigating abstinent smokers who have passed the phase of acute withdrawal. Another study found no influence of smoking quantity but steeper discounting in smokers with a higher level of nicotine dependence measured with the Fagerström Test for Nicotine Dependence (FTND), supporting the second or the third account (Sweitzer et al., 2008). Trait rather than state differences have further been suggested by longitudinal data spanning mid-adolescence to young adulthood (Audrain-McGovern et al., 2009). Hence, temporal discounting was not only stable over time and unaffected by smoking; it even predicted smoking initiation. Moreover, a higher discounting rate was found to be associated with an increased risk for relapse (Goto et al., 2009).

Brain imaging revealed activation of the ventral striatum, hippocampus, posterior cingulate cortex, visual cortex, pre- and supplementary motor areas, the intraparietal cortex, and medial prefrontal regions during intertemporal decision making (McClure et al., 2004). A recent study used an adapted task focussing on the anticipation of immediate and delayed rewards and found striatal hypoactivation during anticipation of delayed rewards in smokers

compared to non-smokers (Luo, Ainslie, Giragosian, & Monterosso, 2011). However, acute effects of nicotine on temporal discounting in humans have neither been investigated on the behavioural nor brain level so far.

In our study we measured brain activation using functional magnetic resonance imaging (fMRI) during the performance of an intertemporal choice task in nicotine-satiated chronic smokers and in non-smokers who received nicotine and matched placebo gums in a double-blinded cross-over design. This allowed us to (1) compare intertemporal decision making and its neural correlates between non-smokers and smokers, (2) investigate the acute effects of a single dose of nicotine on intertemporal decision making in non-smokers, whose reward circuitry has not been chronically exposed to nicotine and who do not experience withdrawal symptoms, and to (3) compare acute and chronic effects of nicotine on a behavioural and neural level. We expected to replicate the frequently reported finding of steeper temporal discounting (i.e., more frequent choice of the early than the delayed amount) in smokers compared with non-smokers. Regarding the acute effects of a single dose of nicotine in non-smokers, we hypothesised an increased preference for early rewards (steeper discounting), as it was shown in rats (Dallery & Locey, 2005; Locey & Dallery, 2009). A shift in temporal discounting would argue for a pharmacological effect of nicotine. As to chronic nicotine effects (via smoking of tobacco in real life) on brain activity, we expected a hyposensitivity in the ventral striatum in response to reward magnitude in smokers (Bühler et al., 2010; Luo et al., 2011). Since decreased activation of the ventral striatum to monetary rewards was shown in adolescents who had only smoked very few cigarette in their lives (Peters et al., 2011), this might be a predisposition in smokers. Animal research has shown that nicotine enhances dopamine release during phasic activity in the striatum (which could be in response to primary rewards and reward predictions) (Rice & Cragg, 2004). As to acute effects of nicotine in the ventral striatum, we therefore expected an increased correlation of the reward magnitude and

activation in the ventral striatum under the influence of nicotine. Regarding effects of chronic and acute nicotine on BOLD signal in other areas of the brain our approach was exploratory.

4.2 Materials and methods

4.2.1 Participants

Thirty-five non-smokers (19 females) and 31 smokers (13 females) were recruited for this study. Participants were 41.3 ± 7.9 (mean, SD) years old (range: 30–60; no significant differences between non-smokers and smokers or females and males). Participants provided informed, written consent according to the declaration of Helsinki. The local ethics committee approved the study. Subjects were recruited by public announcement. Smokers were not seeking treatment but were informed about in-house smoking cessation courses after the study. Inclusion criteria for non-smokers were a maximum lifetime consumption of 20 cigarettes and no nicotine consumption during the past 12 months. Smokers were required to be smoking at least 15 cigarettes per day and had to fulfil DSM criteria for nicotine dependence. To verify the smoking status of participants, we measured expiratory CO levels and serum nicotine and cotinine levels. The Munich-Composite International Diagnostic Interview (Wittchen et al., 1997) was used to assess axis I mental disorders. Exclusion criteria were pregnancy, a lifetime history of substance use disorders (except nicotine dependence for smokers), schizophrenia and bipolar disorder and 12 months prevalence of all other psychiatric disorders. A urine screening test for illicit drugs and for pregnancy was used. Participants were not regularly taking medication and declared not to have taken any medication and not to have consumed any alcohol three days prior to the experiment. All participants were right-handed (laterality quotient in the Edinburgh Handedness Inventory (Oldfield, 1971) > +50) and had a sufficient visual acuity (binocular, corrected ≥ 0.8). There are no data available from two female non-smokers and three male smokers (failed thorough screening, n=4, and withdrawn consent in

the course of the study, n=1). One smoker had to be excluded from the analysis, because the self-report on smoking behaviour was highly incongruent to the physiological parameters (self-report: 20 cigarettes per day; CO-level: 6 parts per million (ppm); nicotine level: 1.51 ng/ml; cotinine level: 52.6 ng/ml; all three physiological parameters more than 2 SD below the mean of the group). Data were collected at the Central institute of mental health, Mannheim, Germany (ZI Mannheim).

4.2.2 Design and drug administration

Smokers underwent one fMRI session. They were advised to smoke as usual and had the opportunity to smoke during the ten to five minutes prior to the fMRI scan in order to prevent withdrawal symptoms during the scan session. Non-smokers underwent two fMRI sessions with a time interval of 7 to 17 days (8.2 ± 2.5) between the two sessions. In each session they received either a commercially available nicotine gum (Nicorette®, 2mg by Pfizer) or a placebo gum with matched taste, consisting of the same ingredients as the nicotine gum except for the nicotine (Placebo by Pfizer) in randomised order in a cross-over design. From the 33 participants who received nicotine and placebo gums, 16 participants received the nicotine gum during their first session. Drug administration was double-blinded. Participants were instructed how to correctly chew the gum. The gum was administered for 30 minutes. Pulse rate and blood pressure were assessed and blood samples were taken approximately 25 minutes after administration of the gum in order to determine nicotine levels and physiological effects. After disposal of the chewing gum, participants were asked which chewing gum they thought they had received.

4.2.3 Functional Magnetic Resonance Imaging

4.2.3.1 Intertemporal Choice Task

To measure neural correlates of temporal discounting while participants had to choose between monetary reward options that varied by delay to delivery, we used an intertemporal choice task similar to the one published by McClure et al. (2004). The task consisted of 40 trials each lasting 20 s in which two options were presented on the left and right side of the screen, with the smaller, earlier amount always presented on the left side. Two yellow triangles underneath each of the money/time pairs indicated that a choice could be made. Participants were given 9 s to choose one of the two money/time pairs. If they did not respond within this time frame, the message "choice too late" appeared on the screen. The earlier amount was chosen by pressing a button with the right index finger, the later amount by pressing a button with the right middle finger. Once the choice had been made, the yellow triangle under the respective money/time pair turned red for 2 s to indicate that the response was recorded. Thereafter, a fixation cross appeared for at least 9 s until the 20 s of the trial were completed. The choice pairs included the combinations immediate vs. 2 weeks, immediate vs. 4 weeks; 2 vs. 4 weeks, 2 vs. 6 weeks; and 4 vs. 6 weeks. The mean early amount was 18.86 ± 7.39 € (range 6.53 – 35.93). The percent difference between the early and the late amount was 1%, 3%, 5%, 10%, 15%, 25%, 35%, or 50% (mean late amount: 22.24 ± 8.88 €, range: 7.18 – 41.32) . The set of choices was prepared and the order was randomly mixed in advance of the study. The same set in the same order was used for each participant. For the exact amounts and the order of presentation see Table S 9.

The task duration was approximately thirteen minutes. At the end of the experiment, one decision was randomly selected and paid to the participant in cash or via bank transfer at the respective time point.

4.2.3.2 fMRI scanning parameters

Scanning was performed with a 3 T whole-body tomograph (Magnetom TRIO; Siemens, Erlangen, Germany) equipped with a standard head coil. For functional imaging, a standard echo-planar image (EPI) sequence was used, repetition time (TR): 2410 ms; echo time (TE): 25 ms; flip angle: 80°. fMRI scans were obtained from 42 transversal slices, orientated 30° clockwise to the anterior commissure-posterior commissure line, with a thickness of 2 mm (1 mm gap), a field of view (FOV) of 192 x 192 mm and an in-plane resolution of 64 x 64 pixels, resulting in a voxel size of 3 x 3 x 2 mm. To exclude structural abnormalities, a 3D T1-weighted magnetization-prepared rapid gradient echo (MPRAGE) image data set was acquired. The scanning time for MPRAGE was approximately six minutes. Images were presented via goggles using MRI Audio/Video Systems (Resonance Technology Inc.). Task presentation and recording of the behavioural responses was performed using Presentation® software (Version 9.90, Neurobehavioral Systems, Inc., Albany, CA, USA).

The scanning session consisted of the intertemporal choice task, an emotion processing task, data published in Kobiella *et al,* (2011), a motivation task (not reported here), and an anatomical brain scan. Depending on whether it was the first or second session (i.e. practice runs for the motivation tasks outside the scanner were conducted or not) the total scanning session lasted between 60 and 90 minutes.

4.2.3.3 Analyses of physiological and behavioural data

Physiological data and behavioural data obtained during the intertemporal choice task were analysed using SPSS (PASW Statistics 17, SPSS Inc., Chicago, IL, USA). Acute nicotine effects on heart rate and blood pressure (systolic and diastolic values) in non-smokers were assessed with repeated-measures analyses of variance (ANOVA) with the within-subject

factor medication (nicotine, placebo) and the between-subject factor order (nicotine first vs. nicotine second). Significance level was set at $\alpha = 5\%$.

To test for differences in discounting behaviour we estimated the individual discount rate for each individual separately from the behavioural data of the fMRI experiment. Previous studies have shown that discounting behaviour can be described in terms of the hyperbolic discount function (Kirby & Marakovic, 1995; Mazur, 1987)

$$V = \frac{A}{1 + k \times D}.$$

In this function V represents the subjective value of a reward, A the amount of a reward, D the delay in weeks, and k the individual discount parameter. We calculated k by estimating individual discount curves for this function using non-linear regression and the ordinary least squares method (OLS) for each subject. Because the discounting parameter k did not follow the normal distribution, computed all statistics with the log transformed k (*log k*). All reported *log k* values are based on delays measured in weeks.

To test for differences in discounting behaviour (*log k*) between smokers and non-smokers, an independent sample t-test was calculated (non-smokers placebo vs. smokers). To test the acute effect of a single dose of nicotine on *log k*, a paired-sample t-test (non-smokers placebo vs. non-smokers nicotine) was calculated. The effect of chronic nicotine intake on discounting (smokers vs. non-smokers nicotine) was tested with an independent sample t-test. Significance level was set at $\alpha = 5\%$ (one-tailed for the smoker – non-smoker (placebo) comparison due to the consistency of previous findings, two-tailed for all other tests). For estimating the effect size for the dependent groups (nicotine-placebo), we used Cohen's d, as it has been shown to be reliable when estimated by using means and standard deviations (Dunlap, Cortina, Vaslow, & Burke, 1996).

Additionally, we tested the immediacy effect according to Figner et al. (2010). This effect is related to a steeper discounting of delayed rewards when one of the alternatives is an immediate option.

4.2.3.4 fMRI data analysis

Imaging data were analysed with Statistical Parametric Mapping (SPM5; Wellcome Department of Imaging Neuroscience, London, UK). Prior to data analysis, functional data underwent preprocessing. The first five images were discarded in order to reduce T1 saturation effects. Data were temporally realigned with descending slice order to minimise temporal differences in slice acquisition. Spatial realignment was performed to correct for head motion over the course of the session. Single subject imaging data was subjected to group statistics if head movement did not exceed 2 mm (translation) and 2 degrees (rotation). Functional data were normalised to a standard EPI template, resampled with a voxel size of 2 x 2 x 2 mm and smoothed using an isotropic Gaussian kernel (8 mm full-width at half-maximum, FWHM).

On the individual level, we modelled the 40 trials (each lasting up to 9 s in which the money/time pairs were presented and the choice for one of them was made) together with the parametric modulators mean magnitude (€) of the rewards of the trial, mean delay of the trial (1 – immediate vs. 2 weeks; 2 – immediate vs. 4 weeks; 3 – 2 weeks vs. 4 weeks; 4 – 2 weeks vs. 6 weeks; 5 – 4 weeks vs. 6 weeks) and choice of the trial (0 – early amount chosen; 1 – late amount chosen) as explanatory variables within the context of the general linear model on a voxel-by-voxel basis. To show brain activation during decision epochs, the effects of mean reward magnitude, mean delay and choice irrespective of acute and chronic nicotine effects, we calculated one-sample t-tests for trial, magnitude, delay and choice and included the respective individual contrast images of all participants and sessions (smokers, non-smokers placebo, non-smokers nicotine, n=85). To test the effect of acute nicotine and to account for the effect of order (nicotine first vs. nicotine second), we ran 4 separate one sample t-tests

(trial, magnitude, delay, and choice; n=28) where the subjects' difference images (nicotine subtracted by placebo) and order, as covariate of no interest, were included. To test the effects of chronic nicotine, individual contrast images of non-smokers placebo (n=31) and smokers (n=25) were included in four separate independent sample t-tests (trial, magnitude, delay and choice) together with the covariate task repetition (1 – task performed for the first time, 2 – task performed for the second time). Furthermore, the same was done using the contrast images of non-smokers nicotine instead of non-smokers placebo. The ventral striatum was an a priori region-of-interest, because it is known to be involved in reward processing. For the effect of reward magnitude we used small-volume correction by centering a sphere of 10 mm in diameter on MNI coordinates reported in the literature to represent reward magnitude (x=8, y=6, z=2 and x=-10, y=4, z=0) (Yacubian et al., 2007). To test the acute and chronic effects of nicotine on processing of reward magnitude in the ventral striatum we used small-volume correction centering a sphere of 10 mm in diameter around the coordinate x=-6, y=12, z=-6, which was shown as peak region reflecting effects of nicotine dependence on processing of reward levels (Bühler et al., 2010). The threshold was $p<0.05$, corrected for family-wise error (FWE) at voxel level.

For the exploration of acute and chronic nicotine effects in other regions of the brain (whole brain analyses), findings were regarded as significant if $p < 0.001$ (uncorrected) in at least 20 contiguous voxels. Effects of task repetition are reported in the Appendix (Table S 10).

Additionally, we tested a model according to McClure *et al.*, (2004). For details see Appendix (section 7.3.1 - 7.3.2 and Figure S 2).

4.3 Results

4.3.1 Physiological data

4.3.1.1 Non-smokers

The mean nicotine level approximately five minutes prior to the scan (i.e. 25 minutes after administration of the chewing gum) was 3.7 ± 1.3 ng/ml (mean, SD). Repeated-measures ANOVAs revealed that both systolic and diastolic blood pressure before the fMRI scan were significantly higher under nicotine compared with placebo (systolic value: $F(1,29)=8.64$, $p=0.006$; nicotine: 125.0 ± 15.2; placebo: 118.7 ± 13.4 and diastolic value: $F(1,29)=8.06$, $p=0.008$; nicotine: 84.8 ± 9.6; placebo: 79.7 ± 11.1). Moreover, heart rates before the fMRI scan tended to be higher under nicotine compared with placebo ($F(1,29)=3.97$, $p=0.056$; nicotine: 74.1 ± 13.3; placebo: 70.2 ± 9.5). At the first session, non-smokers correctly guessed that they received a nicotine gum in 85.3% of the instances. At the second session, their guesses were correct in 87.1%. Both of these values deviated significantly from chance (session 1: $Z(34)= 4.12$, $p < 0.001$; session 2 $Z(31)= 4.13$, $p < 0.001$) demonstrating that despite the double-blinded design, participants were highly accurate in guessing whether they received nicotine or placebo gums.

4.3.1.2 Smokers

On average, smokers smoked 24.5 ± 6.6 (mean, SD) cigarettes per day (range 15–40) and scored 6.1 ± 1.7 points (range 3–10) on the FTND. CO levels on the experimental day were 30.2 ± 10.3 parts per million (ppm). The mean nicotine level prior to the scan was 19.7 ± 6.6 ng/ml, the mean cotinine level was 341.3 ± 102.6 ng/ml. Systolic and diastolic blood pressure before the fMRI scan were 121.9 ± 13.1 and 81.3 ± 8.0, respectively. Heart rate before the fMRI scan was 78.5 ± 9.7.

4.3.2 Behavioural data

In line with previous studies, smokers (mean $(M)_{\log k}$ = -2,90 $week^{-1}$, standard deviation $(SD)_{\log k}$ = 0.66) discounted delayed rewards more steeply than non-smokers ($M_{\log k}$ = -3.28 $week^{-1}$, $SD_{\log k}$ = 0.88), t(58)= -1.92, p=0.029, one-tailed (see Figure 4-1). The difference corresponds to a moderate effect size of Cohen's d = 0.48. A single dose of nicotine in non-smokers ($M_{\log k\_placebo}$ = -3.280.044 $week^{-1}$, $SD_{\log k}$ = 0.88; $M_{\log k\_nicotine}$ = - 3.22 $week^{-1}$, $SD_{\log k}$= 0.76) did not significantly increase the frequency of choosing the early amount: t(30)= -0.66 p=0.52, two-tailed. Corresponding to the non-significant and nominal very small difference between both conditions in non-smokers (placebo and nicotine) the effect size is small as well (Cohen's d = 0.085). Neither did we find an effect of chronic nicotine (smokers vs. nonsmokers nicotine) on reward choices: t(56)= -1.69, p=0.096, two-tailed. The effect size between smokers and non-smokers under nicotine was also moderate (Cohen's d = 0.43).

Although the discounting behaviour of smokers and non-smokers (placebo and nicotine) was more pronounced in trials offering an immediate option (i.e. immediacy effect, Figner et al., 2010) compared to trials offering two delayed options (T(92)=2.935, p<0.01, (two-tailed)), there was no significant nicotine effect (T(30)=1.05, p=0.303) when looking only at this small number of trials (16 out of 40).

The effect of task repetition in non-smokers (interactions between order and medication) was explored and not significant (p > 0.2).

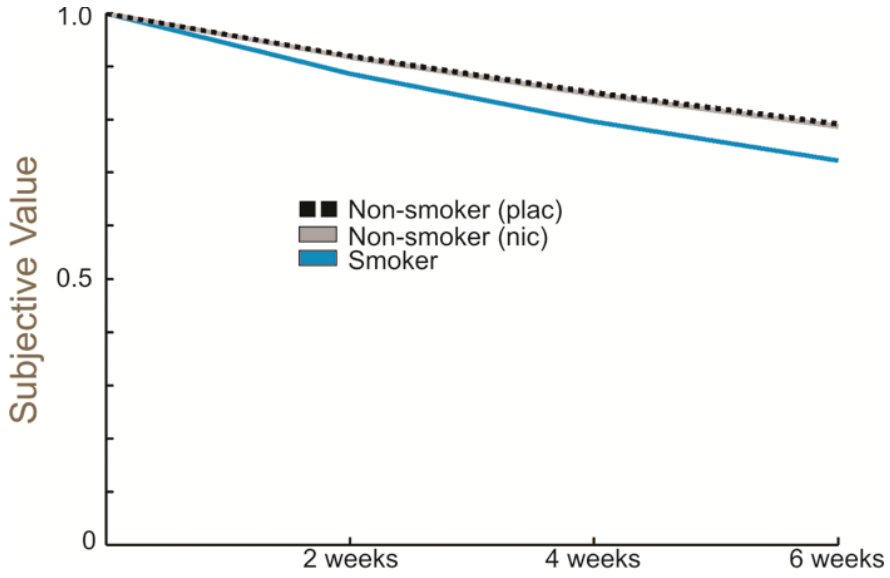

Figure 4-1: Discount functions of the different groups (non-smokers under placebo (black dotted line) and nicotine (grey) and in nicotine-satiated smokers (blue) based on median k, n=31 non-smokers, n=27 smokers).

4.3.3 Imaging data

4.3.3.1 Effects of task

Among a large number of brain regions activated during the decision epochs of the intertemporal choice task, activation was most pronounced in the inferior frontal gyrus, anterior insula, middle cingulate gyrus, supplementary motor area, thalamus, hippocampus, brain regions of the ventral and dorsal visual processing streams and cerebellum (Figure 4-2a).

Mean reward magnitude was positively associated with activation in the ventral striatum (maximum at x=8, y=6, z=2; t=2.67, p = 0.035 FWE corrected at voxel level, Figure 4-2b). The shorter the mean delay to the delivery of the reward the more activation there was in the left superior temporal gyrus and the less activation there was in the bilateral superior occipital gyrus, cuneus, calcarine sulcus and lingual gyrus (Figure 4-2c).

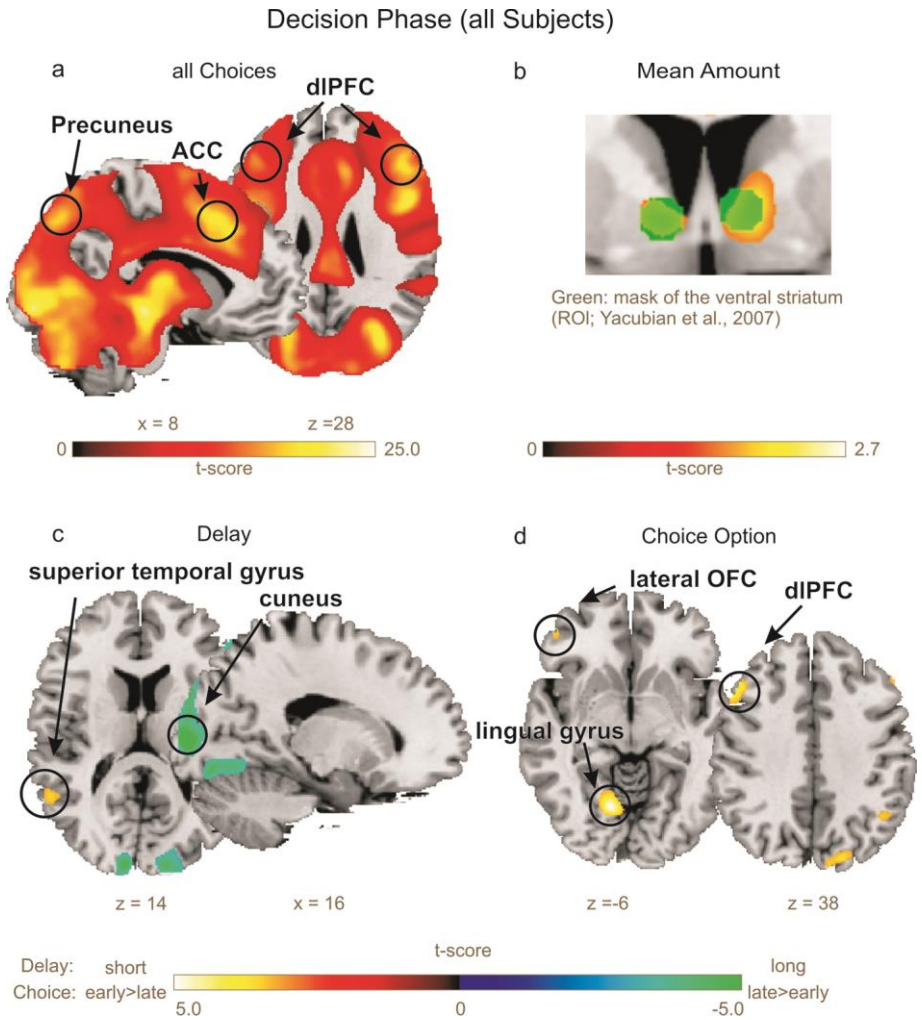

Figure 4-2: Task effects of decision, delay and choice. 4.2a: Areas of the brain which show a higher BOLD signal during decision epoch in each trial (threshold T = 10-5, p<0.05, FWE-corrected) 4.2b: The mean amount of early and late alternatives was positively associated with the BOLD signal in the right ventral striatum. The mask used for small- volume correction was created using coordinates reported by Yacubian et al. 2007 (depicted in green). 4.2c: The shorter the mean delay to reward delivery, the more activation in the superior temporal gyrus and the less activation in the cuneus. 4.2d: Choosing the earlier reward was associated with activation in the left lingual gyrus, left lateral orbitofrontal gyrus (OFC), and left dorsolateral prefrontal gyrus (dlPFC).

The choice of the earlier compared to the later reward was associated with activation in the left lingual gyrus, right cuneus, bilateral calcerine sulcus, left inferior orbitofrontal cortex, bilateral middle frontal gyrus and bilateral inferior frontal gyrus. Choosing the later reward in contrast to the earlier reward did not elicit a significant activation pattern (Figure 4-2d).

4.3.3.2 Effects of chronic nicotine (smokers vs. non-smokers placebo and smokers vs. non-smokers nicotine)

During intertemporal decision-making, smokers compared with non-smokers (placebo) showed significantly less activation in parietal and occipital regions (middle occipital gyrus, fusiform gyrus, lingual gyrus, precuneus, posterior cingulate gyrus, see Figure 4-3a), subcortical structures (caudate and hippocampus), and the cerebellum (Table 4-1a). Smokers showed also less activation in the left and right precuneus (x=-2, y=-68, z=62, t=3.97, k=47; x=12, y=-76, z=56, t=3.84, k=21) compared to non-smokers under acute nicotine (Figure 4-3b).

Non-smokers (placebo) showed a significantly stronger correlation between mean reward magnitude and BOLD response in the left ventral striatum than smokers (x=-4, y=10, z=-10, t=2.90, k=63, p=0.021 FWE), see Figure 4-3e. There was no significant difference between smokers and non-smokers under nicotine (x=-2, y=10, z=-8, t=2.24, k=26, p=0.089 FWE). Smokers did not differ from non-smokers (placebo) regarding their neural response to the mean delay to reward delivery. However, smokers compared to nicotine-exposed non-smokers showed greater activation in the left angular gyrus (x=-44, y=-52, z=26, t=3.71, k=20) with shorter mean delay to the delivery of the reward.

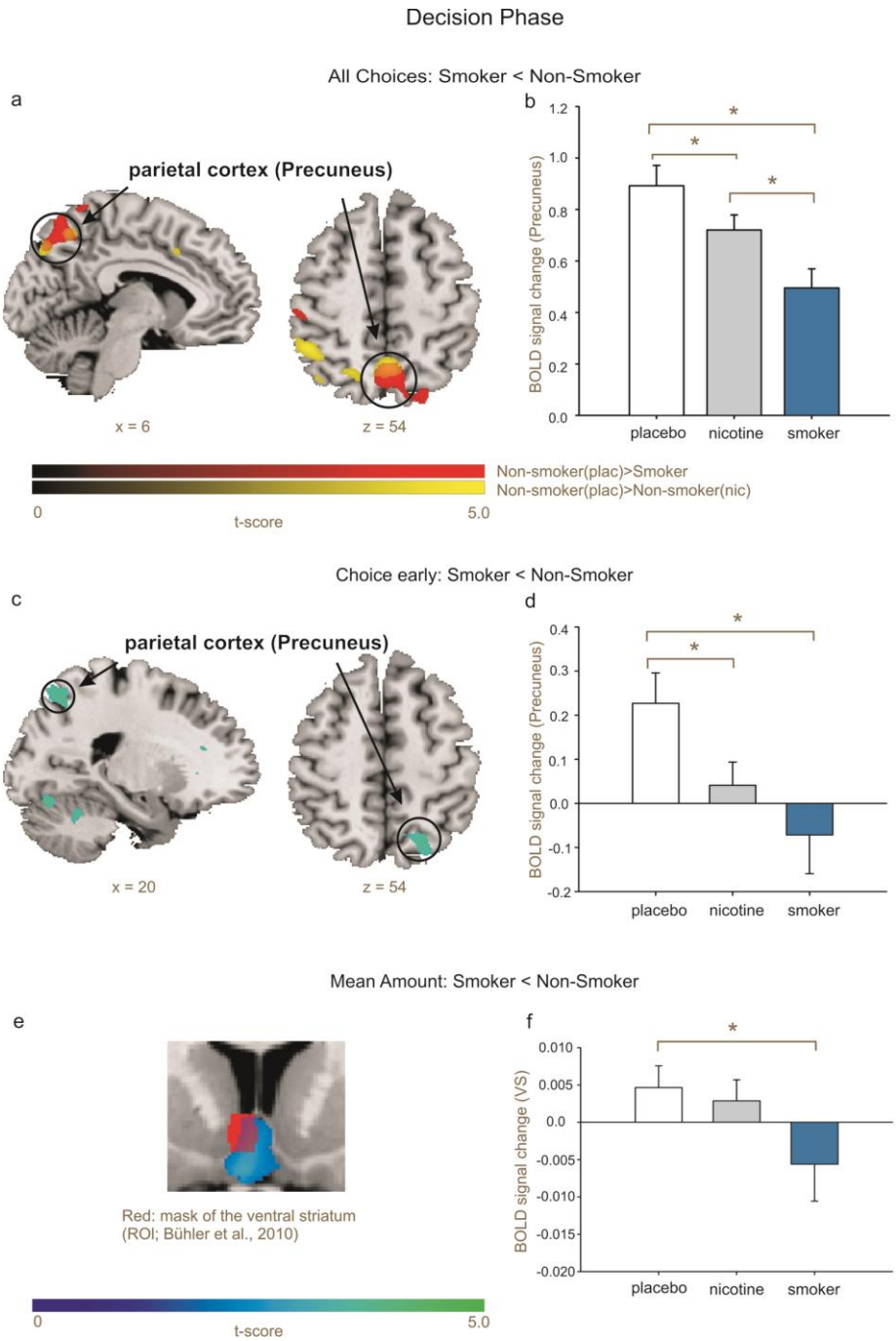

Figure 4-3: Neural differences between smokers and non-smokers. Smokers (red) and non-smokers under nicotine (yellow) compared to non-smokers under placebo showed less activation in the precuneus during intertemporal decision epochs (overlay of both comparisons is depicted in orange, 4.3a), and when choosing the earlier reward (4.3c). Additionally, smokers showed less activation related to the magnitude of the mean amount in the ventral striatum (the mask used for small-volume correction was created using coordinates reported by Bühler et al. 2010, depicted in red.) (4.3e). Plotting the mean BOLD signal change in an anatomical ROI of the precuneus during the decision epochs (4.3b) and the decision for the early reward (4.3d) shows that non-smokers under the influence of nicotine (nicotine, n=29) were in between non-smokers under placebo

Table 4-1: Non-smokers placebo > smokers during (a) decision epochs and (b) choice early>late, threshold p<0.001 uncorr., t>3.25. Clusters indicated with an asterisk survive cluster-level FWE-correction (p < .05)

Region	Side	Cluster Size	MNI coordinates			T_{max}
			X	y	z	
(a) Decision epochs: Non-smokers placebo > smokers						
Middle Occipital Gyrus, Fusiform Gyrus, Lingual Gyrus, Inferior / Middle temporal Gyrus	R	473*	26	-82	2	5.84
Precuneus	R, L	764*	2	-64	52	5.20
Lingual Gyrus, Middle Occipital Gyrus	L	134	-30	-72	2	4.62
Lingual Gyrus, Calcarine	R	50	12	-96	-4	3.99
Insula, Caudate Tail, Hippocampus, Parahippocampal Gyrus	L	575*	-30	-36	18	4.34
Caudate Head	R	36	20	28	0	3.85
Caudate Body	R	37	22	-10	28	3.77
Caudate Head	L	64	-20	26	0	3.72
Posterior Cingulate Gyrus, Superior Temporal Gyrus	R	152	26	-46	28	3.83
Postcentral Gyrus	L	24	-52	-28	56	3.74
Cerebellum (Declive, Tuber)	R	45	46	-74	-28	4.03
Cerebellum, Tuber	L	92	-34	-54	-38	3.81
(b) Choice (early>late): Non-smokers placebo > smokers						
Cerebellum; Declive, Culmen	R	332	28	-60	-30	4.34
Cerebellum, Culmen; Fusiform Gyrus	L	201	-36	-40	-28	4.20
Lingual Gyrus	R	164	26	-76	-14	4.07
Lingual Gyrus; Cerebellum (Declive)	R	104	4	-76	-12	3.58
Precuneus, Superior Parietal Lobule	R	158	20	-64	52	3.86
Cuneus	R	63	12	-82	18	3.95
Precentral Gyrus	R	104	64	4	8	4.02
Inferior Frontal Gyrus	R		62	16	20	3.71
Superior Temporal Gyrus	R		54	2	6	3.42
Superior Temporal Gyrus	L	44	-44	16	-24	3.87
Middle Temporal Gyrus	R	42	60	-64	10	4.03
Middle Temporal Gyrus	L	50	-36	-60	10	4.01
Anterior Cingulate Gyrus	L, R	268	-2	34	10	3.91
Caudate	R		14	22	2	3.80
Anterior Cingulate	R	25	16	30	18	3.68
Medial Frontal Gyrus	R	67	10	44	22	3.80
Postcentral Gyrus	R	113	32	-42	74	3.61
Postcentral Gyrus	R	23	26	-40	48	3.71
Parahippocampal Gyrus	L	20	-28	-22	-22	3.70
Claustrum	L	24	-26	18	6	3.61
Insula	R	22	40	-18	-12	3.52

When choosing the earlier reward, smokers compared with non-smokers (placebo) showed decreased brain activation amongst other regions in the bilateral cerebellum, precuneus, anterior cingulate gyrus, and right caudate head (Figure 4-3c, Table 4-1b). Smokers compared to non-smokers (nicotine) showed decreased activation in the left and right medial frontal gyrus (x=-12, y=34, z=-12, t=3.91, k=34 and x=8, y=38, z=-14, t=3.9, k=24) and in the

right cuneus (x=8, y=-84, z=16, t=3.60, k=36) when choosing the earlier reward (Figure 4-3d).

4.3.3.3 Effects of acute nicotine (non-smokers placebo vs. non-smokers nicotine)

The comparison of the non-smoker's intertemporal decision epochs under nicotine and placebo showed decreased activation under nicotine compared with placebo in occipital and parietal regions (lingual gyrus, middle occipital gyrus, fusiform gyrus, precuneus), frontal regions (inferior frontal gyrus, cingulate gyrus) and subcortical regions (hippocampus, caudate tail; Table 4-2a). Interestingly, this pattern of activation resembles the contrast between smokers and non-smokers, placebo (Table 4-1a, Figure 4-3a and b).

Table 4-2: Non-smokers placebo > nicotine during (a) decision epochs, and (b) processing of reward magnitude, threshold p<0.001 uncorr., t>3.43. Clusters indicated with an asterisk survive cluster-level FWE-correction (p < .05)

Region	Side	Cluster Size	MNI coordinates			T_{max}
			x	y	z	
(a) Decision epochs: placebo > nicotine						
Lingual Gyrus, Middle Occipital Gyrus	R	224	32	-74	-2	5.56
Fusiform Gyrus	L	56	-34	-50	-12	4.45
Precuneus, Superior Parietal Lobule	L, R	397*	0	-58	54	4.88
Precuneus	R	307*	14	-72	46	4.77
Inferior Parietal Lobule	L	241*	-46	-48	54	4.69
Claustrum	L	48	-28	14	12	4.65
Claustrum	R	23	24	22	-8	4.24
Inferior Frontal Gyrus	R	62	40	12	26	4.24
Middle Frontal Gyrus	L	20	-36	36	8	4.16
Cingulate Gyrus	R	35	4	14	40	3.86
Hippocampus	R	30	32	-32	-4	4.10
Parahippocampal Gyrus	R	23	34	-54	-8	3.97
Caudate Tail	L	157	-28	-40	6	4.04
Superior Temporal Gyrus	R	27	36	-42	8	3.86
(b) Reward magnitude: placebo < nicotine						
Superior Temporal Gyrus, Anterior Insula	L	242*	-36	2	-14	5.50
Amygdala, Hippocampus	L		-26	-6	-16	4.71
Postcentral Gyrus	L	32	-64	-14	30	4.01
Cerebellum	L	59	-4	-34	-40	5.52
Cerebellum	L	40	-10	-26	-22	4.40

Nicotine effects on processing of mean reward magnitude in the ventral striatum were not significant. However, non-smokers under nicotine showed increasing activation with the

mean amount of reward options in the left hippocampus (Figure 4-4a and b) and neighbouring amygdala as well as the left anterior insula (amongst other regions,

Table 4-2b). There were no significant nicotine effects on processing of mean delay to the delivery of the reward and reward choice.

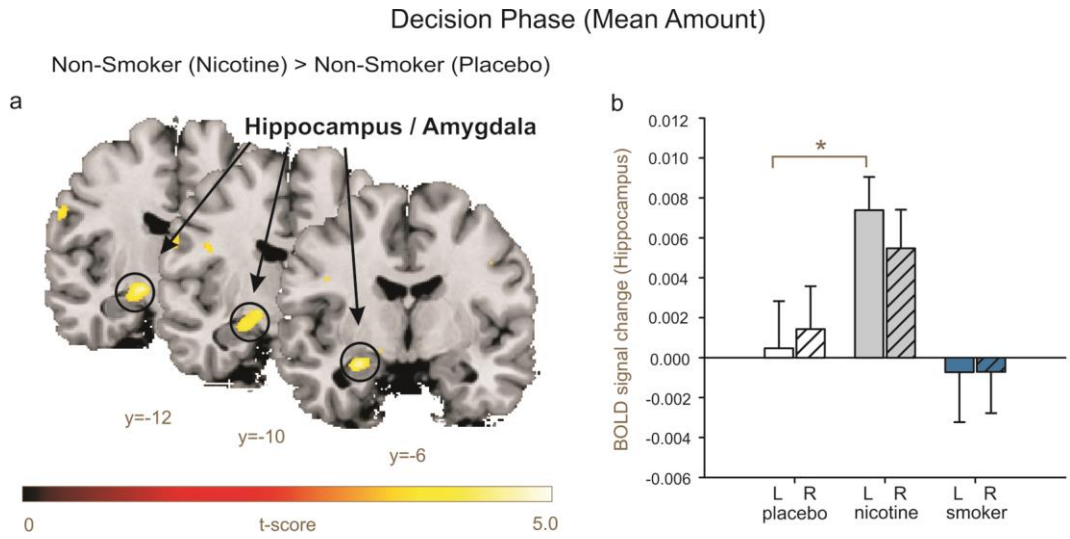

Figure 4-4: Acute nicotine effects in the non-smokers' brain. 4.4a and 4.4b: Non-smokers exposed to 2 mg nicotine compared to non-smokers (placebo) showed increased left hippocampal / amygdala activation with higher mean amounts of early and late reward options. 4.4b: Association between mean amount of early and late alternatives and hippocampal BOLD signal change plotted for non-smokers placebo (placebo), non-smokers nicotine (nicotine) and nicotine-satiated smokers (smokers); filled bars = left hippocampus, dashed bars = right hippocampus; L = left, R = right. Error bars indicate + 1 SEM. n=31 non-smokers placebo, n=29 non-smokers nicotine, n=25 smokers.

4.4 Discussion

In the present study, we aimed to disclose the effects of acute nicotine in non-smokers and chronic nicotine in smokers on neural correlates of temporal discounting. Hence, we measured behaviour and brain activation while nicotine-satiated smokers and non-smokers exposed to nicotine and placebo performed an intertemporal choice task.

We replicated the finding that smokers discount monetary rewards more steeply than non-smokers as indicated by a higher preference of smaller and earlier over larger and later monetary rewards. Compared to some of the previous studies in the field, the magnitude of the difference between smokers and non-smokers was similar (Mitchell, 1999; Sweitzer et al.,

2008). However, other studies showed a more pronounced difference between smokers and non-smokers (Bickel et al., 1999; Reynolds, 2004). Interestingly, those differences in behaviour were reflected in the brain response during the decision epochs of the experiment: Smokers differed significantly from non-smokers showing less activation in parietal and occipital areas (e.g. in the precuneus). Involvement of parietal brain areas in inter-temporal decision making has been shown before (Boettiger et al., 2007; McClure et al., 2004; Monterosso et al., 2007; Ripke et al., 2012). McClure *et al.* (2004) reported an association between more self-controlled and patient decisions and BOLD response in the parietal lobe. Additionally, the precuneus is associated with self-processing (Cavanna & Trimble, 2006). Thus, smokers may prefer earlier rewards because it is harder for them to anticipate the gain of the additional but delayed reward, reflected in less activation in the parietal lobe. Besides, the precuneus has been implicated in approximate arithmetics (Dehaene et al., 1999), number comparison (Pesenti, Thioux, Seron, & De Volder, 2000; Pinel, Dehaene, Riviere, & LeBihan, 2001) and more general attention orienting processes in space, time and number (Dehaene et al., 2003), i.e. processes which are required in weighing up the reward options.

In addition, we are first to investigate acute effects of nicotine on discounting behaviour and underlying neural correlates in humans. We found that nicotine did not alter non-smokers' behaviour during intertemporal choice. As to the neural correlates of intertemporal decision making, we demonstrated that a single dose of nicotine decreased activation in the precuneus and lingual gyrus in non-smokers, i.e. in the same regions in which the chronic nicotine effect in smokers was found. In line with our finding of a nicotine-induced deactivation, attention-related decreases in frontal, parietal and occipital regions (including the precuneus) have been previously reported (Hahn et al., 2007; Hahn et al., 2009). Interestingly, parietal deactivation under nicotine was associated with performance improvements in the attention task, possibly due to inhibition of task-independent brain processes. Notably, however,

other previous studies applying acute nicotine reported increased neural activation amongst others in the precuneus (e.g. Stein *et al.* (1998) during resting state; Hong *et al*. (2009) & Lawrence *et al.* (2002) during rapid visual information processing).

Given the fact that nicotine levels in smokers were 5-fold higher than in nicotine-satiated non-smokers, it seems reasonable to assume that group differences between smokers and non-smokers could be attributable to acute pharmacological effects of nicotine. Whereas differences in neural activation between nicotine and placebo sessions were evident for non-smokers, the effects of a single dose of nicotine were very small on the behavioural level. This might indicate that nicotine triggers different processes in the brain that counteract each other and thus mask behavioural effects. For example, if acute nicotine increases the subjective value of high rewards as suggested by Anderson and Diller (2010), it may promote choices for delayed rewards because delay is usually correlated with reward magnitude. Another alternative is that neural patterns of activation are more sensitive to effects of nicotine whereas higher doses of nicotine may be required to affect behavioural choices. However, we do not believe that group differences are solely due to pharmacological effects of nicotine, because nicotine dependent smokers have developed substantial tolerance to nicotine, resulting in a need for higher doses to yield the same effects. Accordingly, group differences may be additionally promoted by other tobacco components or a self-selection bias. To neatly investigate the pharmacological effect of nicotine, it would be necessary to repeatedly administer different doses of nicotine in nicotine-naïve subjects. Due to ethical reasons, this cannot be accomplished in humans. However, previous studies with rats have investigated the acute and repeated effects of nicotine on intertemporal choice (Anderson & Diller, 2010; Dallery & Locey, 2005). Dallery and Locey (2005) found that acute injections of nicotine in rats dose-dependently increased preference for small immediate reinforcers over large delayed reinforcers. Moreover, rats chronically exposed to nicotine showed long-lasting, but reversible in-

creases in impulsive choice. In later studies, the authors argued that this effect may be due to nicotine decreasing the sensitivity to the reward magnitude (or in other words to increasing the value of small rewards) rather than to alter the impact of differences in delays (Locey & Dallery, 2009; Locey & Dallery, 2011). In contrast to this, Anderson and Diller (2010) found that acute nicotine decreased impulsive choices, whereas repeated exposure to nicotine yielded predrug-like effects. Despite conflicting results both studies indicate that acute and repeated nicotine effects on impulsive choice were reversible in rats.

Contrary to our hypothesis, we did not find an acute nicotine effect in the ventral striatum of non-smokers during processing of the reward value of money/time pairs. However, an acute nicotine effect was found in different regions: the higher the mean amount, the stronger the brain activation under nicotine in the left hippocampus, amygdala, and anterior insula. The hippocampus is a critical structure to integrate value and delay information (Mchugh, Campbell, Taylor, Rawlins, & Bannerman, 2008) and the amygdala may subserve this process by signalling higher relevance (Ousdal, Reckless, Server, Andreassen, & Jensen, 2012). Notably, the hippocampus and the amygdala contain high densities of nicotinic acetylcholine receptors (Gotti, Zoli, & Clementi, 2006) and, together with the insula, have been implicated in acute pharmacological effects of nicotine on brain activity (Domino et al., 2000; Rose et al., 2003; Stein et al., 1998; Zubieta et al., 2001), rendering our results highly plausible. This nicotine effect of increased reward value processing in the hippocampus and amygdala was only found in non-smokers and not in smokers. Thus, this finding is in line with results of Anderson and Diller (2010): Initially, acute nicotine effects on reward magnitude may counter impulsive behavioural choices whereas chronic administration could attenuate this effect. It is tempting to hypothesise that this may foster smoking initiation in adolescents with initially steep temporal discounting while not producing substantial differences in discounting after chronic drug use (Audrain-McGovern et al., 2009).

In accordance with previous studies, the mean reward magnitude was positively associated with activation in the ventral striatum (Kable & Glimcher, 2007; Peters & Buchel, 2010). Moreover, in line with our hypothesis we found that this reward reactivity was significantly stronger in non-smokers than in smokers. Bühler and colleagues (2010) found that chronic smokers showed reduced striatal activation to reward-predicting cues compared to occasional smokers. Furthermore, in line with our results, striatal hypoactivation has been reported during anticipation of delayed rewards in smokers compared to non-smokers using an adapted monetary incentive delay task with a focus on anticipation of immediate and delayed rewards (Luo et al., 2011) as well as during processing of temporal difference errors when compared to non-smokers (Rose et al., 2011). Findings of lower ventral striatal activation in adolescents who smoked fewer than ten cigarettes in their lives (Peters et al., 2011) indicate that ventral striatal hyposensitivity might predispose individuals to initiate nicotine use. Thus, in smokers nicotine intake via smoking might be a strategy to compensate ventral striatal hyposensitivity by amplifying reward-related dopamine signals (Rice & Cragg 2004), even though this was not reflected in our non-smokers' data, which did not reveal increased ventral striatal response to reward magnitude under nicotine.

Failure of the double-blindedness is a limitation of the present study. Future imaging studies could use other forms of nicotine delivery (e.g. patches) where nicotine effects may not be so easily detectable. Moreover, even though the order of nicotine administration was randomised and the neural effects of task repetition were accounted for, it is a methodological limitation that smokers performed the task only once, whereas non-smokers completed the experiment twice. As a consequence, non-smokers performed the same set of trials on two occasions. Possibly, they remembered those trials from the previous testing session and made consistent choices. If so, potential behavioural differences between the placebo and the nicotine condition might have been masked. Thus, future studies investigating the same partici-

pants on several occasions should apply a parallel task with a different set of trials. Additionally, we believe that an adaptive intertemporal choice task would allow a more precise estimation of the individual discount rate and could hence be more sensitive to pharmacological effects. Moreover, higher nicotine doses might be needed to bring behavioural differences forward. Because repeated nicotine administration in different doses is ethically questionable in non-smokers, future studies could administer different doses of nicotine in occasional smokers who are strongly resilient to nicotine dependence and, consequently, do not experience withdrawal symptoms which might interfere with acute nicotine effects.

Altogether, in our study we replicated differences in discounting of delayed rewards between smokers and non-smokers and, for the first time, demonstrated differences in the underlying neural processes. The administration of a single dose of nicotine in non-smokers altered brain activation but did not impact behaviour. Our results do not preclude that pharmacological effects of repeated nicotine administration may contribute to the differences in discounting between smokers and non-smokers, because acute nicotine effects resembled chronic nicotine effects but were smaller in magnitude. However, because tolerance likely levels potentially larger effects of higher doses in chronic smokers, we conclude that cross-sectional differences between smokers and non-smokers might not only be due to acute pharmacological effects of nicotine. Longitudinal studies are needed to investigate predrug group characteristics as well as consequences of smoking on discounting behaviour and its neural correlates.

5 General Discussion

The work at hand was done to contribute to a better understanding of reward decision making which is of relevance for health-related behaviour as shown in chapter 1.1. Therefore an intertemporal choice task as a paradigm for reward decision making was conducted in all three studies of this thesis. Neural correlates of reward processing and decision making were tested in their relation to the discount rate as a behavioural measure of impulsivity (please note that in the following discussion the term impulsivity refers to the individual discount rate and will be used synonymously) and consistency of choices. Further, both behavioural measures have been tested with regard to their link to age, intelligence and nicotine intake (i.e. acute and chronic) to exemplify their associations with health-related risk and protective factors. Moreover, neural correlates underlying these associations have been revealed.

As a result it has been shown that the discount rate and the consistency of choices develop from mid-adolescence to young adulthood (i.e. decreasing discount rate and increasing consistency). Differences regarding reward processing were more sensitive to the individual discount rate than to chronological age, whereas differences during decision processing were related to changes in consistency and age. Additionally, it has been shown that neural processes in brain areas which are related to higher crystallised intelligence are linked to the individual discount rate and consistency during intertemporal choices. As addiction was exemplarily chosen to investigate health-related behaviour, neural processes of intertemporal choices were tested under acute and chronic nicotine. Although chronic effects of smoking on the neural level were stronger than acute effects of nicotine intake, acute nicotine intake affected the non-smoker's brain in the same brain areas.

The next sections will first discuss the results of all three studies separately followed by an integrative approach and future perspectives.

5.1 Effects of age on the behavioural and neural level

The main finding of *study 1* confirmed that adolescents were behaviourally more impulsive than adults, but that there was no difference in neural processing of delayed rewards. The lack of differences between adults and adolescents was due to the design of the intertemporal choice task we used in our study. Importantly, all presented rewards during the task were adapted to the subjects' individual discount rate. A higher individual discount rate, independently of age, was related to lower BOLD signal evoked by delayed rewards in the ventral striatum. The finding implicates that differences during the neural processing of reward value are more sensitive to the individual discount rate than to chronological age. These results have direct implications for studies which compare reward processing in adults and adolescents. These studies should consider the discount rate as a confounding individual variable, because it differs between adults and adolescents and is associated with reward value processing in the brain.

During the decision making process, which was the second aspect investigated regarding age differences in reward decision making, adults showed higher BOLD response than adolescents in the superior and inferior parietal cortex. These regions are discussed as playing a role in intertemporal decision making, independently of the reward value (Boettiger et al., 2007; McClure et al., 2004; Monterosso & Ainslie, 2007). The BOLD differences in the parietal network might be due to not yet matured brain areas in adolescents. At the same time adolescents were less consistent in their decisions. One could speculate that due to the already matured parietal decision network in young adults the comparison of reward choices was more precise in young adults compared to adolescents at age 14. Testing the association between consistency of choices and BOLD response during the decision making phase, revealed that brain responses in the same parietal areas, as well as in the DLPFC (i.e. fronto-parietal decision network) and the thalamus were positively correlated with the behavioural consisten-

cy of choices. Therefore lower consistency of intertemporal choices might indicate ongoing maturation of parietal brain areas in adolescents.

The data of *study 1* can also be interpreted in line with theories regarding adolescent brain development which state that subcortical brain areas mature first and cortical brain areas (especially the prefrontal cortex) mature later during adolescence (Casey et al., 2005; 2008; Steinberg, 2005). This maturational gap has been interpreted as a reason for risky behaviour of adolescents including health-related behaviour (e.g., substance use; cf. Crone & Dahl, 2012). Here the differences in the ventral striatum were rather associated to the discount rate than to age indicating that the maturation in this structure might be completed in mid-adolescence (age 14). In contrast, activation in cortical brain areas during decisions differed between adults and adolescents indicating ongoing maturation which is behaviourally related to less consistent decision making in adolescents.

5.2 Effects of intelligence on the behavioural and neural level in adolescents

The main finding of *study 2* was that activity in the same brain areas was associated to crystallised intelligence as well as to the behavioural outcomes of intertemporal choice in an adolescent sample.

Higher crystallised intelligence was associated with higher BOLD in the fronto-parietal decision network during the decision making phase of the intertemporal choice task. This finding was consistent with the parieto-frontal integration theory (P-FIT, Jung & Haier, 2007; Colom et al., 2009). The theory states that a parieto-frontal network, supported by occipital and temporal brain regions, is functionally and structurally related to performance in tasks which require g-factor intelligence (i.e. reasoning- or working memory tasks). In *study* 2 higher BOLD which was related to higher crystallised intelligence was at the same time related to more consistent decisions. Thus, the intelligence related activity in the fronto-parietal

network of the brain was related to more precise decisions during the task. In the light of the efficiency model (Haier et al., 1992; Tang et al., 2010), which states more efficient brain processing (i.e. lower BOLD response is associated with same performance) to be related to higher intelligence, this might implicate that not only more efficient processing leads to the same performance as in less intelligent individuals, but that additionally higher BOLD response is related to better performance. This is also in line with the resources theory (i.e. using more resources during the task leads to better performance, Bunge et al., 2000) and findings that more intelligent individuals perform better while investing more resources (Lamm et al., 2001). Here, more intelligent subjects distributed more resources to the task and were more consistent in their decisions.

As to processing of delayed reward value during intertemporal choices, it has been shown that higher BOLD in a frontal network, consisting of the inferior frontal gyrus (IFG) and the anterior cingulate cortex (ACC), was related to higher crystallised intelligence measures. Activity of the IFG is related to response inhibition (for a meta-analysis see Swick et al., 2011) and patient intertemporal choices (Luo et al., 2012) in previous studies, whereas the anterior cingulate cortex is related to conflict monitoring (for a review see Botvinick, Cohen, & Carter, 2004). Consistently, in more intelligent individuals the higher BOLD in the IFG part of this network was related to less impulsive decisions during an intertemporal choice task. Thus, differences in crystallised intelligence might lead to less impulsive behaviour via this brain behaviour relation. Interestingly, these associations might provide a mechanism how environmental factors influence the discount rate. The data of *study 2* revealed that the education level of the participants' parents was positively correlated to crystallised intelligence and negatively to the discount rate. Neural correlates mediating the association between crystallised intelligence and discounting might also mediate the influence of such an environmental factor. The protective effect of education, which is related to less substance use

(Jaroni et al., 2004) might also be based on the association between crystallised intelligence and the discount rate.

5.3 Effects of smoking and nicotine on the behavioural and neural level

The main finding of *study 3* was that the acute effect of nicotine intake in non-smokers occurred in the same brain regions as has been found in smokers compared to non-smokers. During intertemporal choices smokers showed a weakened brain response in the parietal cortex (i.e. in the precuneus), which has been shown in previous studies to be related to intertemporal decision making (Boettiger et al., 2007; McClure et al., 2004; Monterosso & Ainslie, 2007). For example McClure *et al.* (2004) reported an association between more self-controlled and patient decisions and BOLD response in the parietal lobe. Additionally, the precuneus is associated with self-processing (Cavanna & Trimble, 2006). Thus, smokers may prefer earlier rewards because it is harder for them to anticipate the gain of the higher but delayed reward, reflected in less activation in the parietal lobe.

No significant nicotine effect on the discount rate was observed in non-smokers. Nevertheless, the results do not preclude that pharmacological effects of repeated nicotine administration in smokers may contribute to the differences in discounting between smokers and non-smokers. The imaging data support this hypothesis, because acute nicotine effects resembled chronic nicotine effects but were smaller in magnitude. However, because tolerance likely levels potentially larger effects of higher doses in chronic smokers, it was concluded that cross-sectional differences between smokers and non-smokers might not only be due to acute pharmacological effects of nicotine.

5.4 Integration approach: Findings of study 1, study 2 and study 3 and the relation to the Competing Neurobehavioural Systems Theory (CNDS Theory)

All three studies of the current thesis aimed at investigating the associations of several variables, such as age, intelligence, nicotine, discount rate and choice consistency on reward decision making, which is relevant for health-related behaviour. The task that was used in all three studies was an intertemporal choice task. Please note that the task was not the same in all three studies of the thesis. In *Study 1* and *2*, the task was designed according to the task used by Kable & Glimcher (2007). For *study 3* a task similar to the one used by McClure *et al.*(2004) was conducted. Nevertheless, it was possible to investigate the effects of all observed variables on the discount rate as well as on neural mechanisms underlying inter-temporal choices. Additionally, in *study 1* and *2* consistency of choices has been tested re-garding the association to age, intelligence and brain function. A further aim was to extend the CNDS theory (Bechara, 2005; Bickel et al., 2007; 2012) with regard to an exemplary risk factor (i.e. adolescent age) and an exemplary protective factor (i.e. higher intelligence).

A finding all three studies had in common was the involvement of a parietal network, consisting of superior, posterior and inferior parietal brain areas, in the neural processing of intertemporal decisions. A higher BOLD response in this network was positively related to age (*study 1*) and higher crystallised intelligence scores (*study 2*). In contrast a lower BOLD was related to smoking and to acute nicotine administration (*study 3*). The fact that a higher BOLD response in the parietal network was further related to more consistent decisions might implicate that the parietal network contributes to more precise decisions. As indicated in chapter 1.2.2 the role of consistency in health behaviour is not clear. Because lower con-sistency might be related to more exploration, the fact that adolescents are less consistent is not surprising. Since adolescence is a period of novel experiences behaving highly consistent

could be disadvantageous. On the other hand, higher consistency could be supportive during smoking cessation as proposed by Luo *et al.* (2012). Consequently, smokers who are less consistent might have more difficulties during cessation. Unfortunately, it could not be tested in *study 3* how behavioural consistency might be related to smoking and nicotine administration. One can only speculate that the higher BOLD response in the parietal network might contribute to deciding consistently for the delayed reward of keeping healthy. But further studies have to test the role of consistency in addiction and the cessation process.

Regarding reward value processing, the results of the *study 1*, *2* and *3* pointed to different brain networks which were related to age, intelligence and smoking. *Study 1* showed that reward value processing was related to inter-individual discount rate differences. The ventral striatum of individuals, who discounted the value of delayed rewards more steeply, seemed to be hyposensitive to delayed rewards. The results of *study 2* revealed an association between higher crystallised intelligence and higher BOLD response during value processing in a frontal network consisting of the IFG and the ACC. Moreover, the higher BOLD response in the IFG was related to lower individual discounting of delayed rewards. *Study 3* revealed that smokers compared to non-smokers showed ventral striatal hyporesponsivity related to reward values. This could indicate that adolescents compared to adults as well as smokers compared to non-smokers might be more impulsive due to the hyporesponsivity of the ventral striatum towards delayed rewards. On the other hand, more intelligent individuals seem to be less impulsive regarding delayed rewards which might be explained by higher involvement of inhibiting and controlling brain areas (IFG and ACC).

This finding might have implications for health-related behaviour and might explain how the tested exemplary risk and protective factors are related to smoking initiation via brain behaviour relations. It has been shown that adolescents are at high risk to initiate substance use (Palmer et al., 2009). Additionally it has been shown that early onset of smoking is a

known risk factor for smoking in adulthood (Behrendt, Wittchen, Hofler, Lieb, & Beesdo, 2009; Taioli & Wynder, 1991). In contrast, higher crystallised intelligence might be a protective factor. Indeed, it has been shown in a previous study that higher educational achievements prevented adolescents from becoming persistent smokers later in life (Jefferis et al., 2003). Thus, even if adolescents are prone to test smoking because they are more impulsive than adults, the more intelligent adolescents might be at lower risk to become addicted. The current thesis contributes to the understanding of possible underlying neural processes of risk and protection factors. On the one hand, hyposensitivity in the adolescent ventral striatum is associated to a higher discount rate (*study 1*) and a higher risk for smoking initiation (Peters et al., 2011). High discount rates might not only account for differences between adolescents and adults but also for individual differences in smoking behaviour between adolescents. Support for this notion comes from a recent study showing that adolescents who at least smoked one cigarette in life discounted delayed rewards more steeply than their never-smoking peers (Peters et al., 2011). Thus, the adolescents' elevated risk to initiate smoking compared to adults due to higher discount rates might be even more elevated when they discount delayed rewards more steeply compared to other adolescents. On the other hand, higher activation in the IFG and the ACC in more intelligent individuals during reward value processing might enhance behavioural inhibition and control and, hence, might support decisions for long-term outcomes as shown in *study 2*. Long-term orientation regarding health-related behaviour might prevent nicotine addiction. Thus, a higher BOLD in this network might be one possible neural correlate of the exemplary protective factor of intelligence. Recently, lower resting state connectivity strength in a network of the IFG, the ACC and the striatum was associated with severity of nicotine addiction in schizophrenic patients and healthy controls (Moran, Sampath, Stein, & Hong, 2012). Further support for a potential role of this network regarding nicotine addiction comes from a study showing that craving can be reduced

by cognitive reappraisal and that the activation of the dorsal ACC was negatively correlated with subjective craving in smokers (Zhao et al., 2012). Brain activation in this network might also provide a mechanism how environmental factors, such as parental education possibly influence the discount rate of adolescents and subsequently health behaviour as mentioned in section 5.2.

Although data of *study 3* showed that the ventral striatum of smokers compared to non-smokers was hyporesponsive towards the magnitude of rewards and discounted delayed rewards more steeply, the question whether this is a pre-drug characteristic or a consequence of smoking or both is still open. Further studies have to clarify those associations in longitudinal samples, which would enable to observe the transition into nicotine addiction before it manifests.

The results of the thesis at hand can also be interpreted in the light of the CNDS theory, which proposes an imbalance between impulsive and executive brain systems leading to addiction and other diseases (Bechara, 2005; Bickel et al., 2007; Bickel et al., 2012). The impulsive system is a subcortical system. Consistent with this theory the risk factors investigated in the current thesis (i.e. younger age, higher discount rate) were associated with responsivity of the ventral striatum. In contrast to the current findings, the CNDS theory proposes hypersensitivity of the ventral striatum. One possible reason might be that the data of the current thesis refer to responsivity towards delayed rewards. Thus, hyposensitivity to delayed rewards in contrast to the immediate rewarding effects of substance use might lead to outweighing the rewarding effects of being healthy in the future. Regarding the protective factors (i.e. higher intelligence) the current work has shown that they were related to higher brain activation in cortical brain areas, such as the IFG as a part of the prefrontal cortex and the ACC, which were formerly shown to be related to inhibition of prepotent responses (Aron et al., 2004; Botvinick et al., 2004; Swick et al., 2011). Regarding intertemporal choices, a higher BOLD

in the IFG has been shown to be related to the inhibition of the prepotent immediate choice (Ballard & Knutson, 2009) and to the choice of the delayed reward (Luo et al., 2012). Additionally, a higher BOLD response in a fronto-parietal network was found in adults compared to adolescents (*study 1*) as well as in more intelligent adolescents (*study 2*) and in non-smokers (*study 3*). Such a network was proposed as the executive brain system preventing impulsive choices (Bechara, 2005; Bickel et al., 2007; Bickel et al., 2012). The data of the current *studies 1* and *2* revealed that the BOLD response in the parietal part of this network was related to more consistent decisions and rather than to less impulsive choices, which was found in *study 3*. Whereas the role of steeper discounting in health-related behaviour, such as addiction is quite clear (e.g. Bickel et al., 2012), the role of consistency has to be further investigated. As outlined before, choice consistency might affect the success of smoking cessation, because the evaluation of outcome values (i.e. nicotine effect vs. anticipating future health) should be stable over time and situations. For instance, ex-smokers should abstain from smoking a cigarette at home as well as in a situation, such as going out with friends who smoke. In the studies of this thesis consistency was negatively related to an exemplary risk factor (i.e. adolescent age) and positively to an exemplary protective factor (i.e. higher intelligence). Additionally, a brain network which is functionally associated to consistency has been shown. However, the role of consistency is very speculative because of the lack of data regarding this behavioural measure. Nevertheless, the findings might extend the CNDS theory regarding an additional behavioural measure of intertemporal choices (i.e. consistency) and the underlying neural processes of possible risk and protective factors.

5.5 Related work

The data collection for *study 1* and *study 2* was part of the project ("The adolescent brain: Development of volitional executive and affect regulating systems"), funded by the German Ministry of Education and Science (BMBF) and the IMAGEN project ("Reinforce-

ment-related behaviour in normal brain function and psychopathology"), funded by the European Commission (Schumann et al., 2010). Several related results emerged from this data collection. This chapter will summarise some of the thematically related ones which are not part of the current thesis.

One study (Müller et al., 2013) showed that prenatal exposure to nicotine (i.e. when the mother smoked during pregnancy) alters the response to anticipation of rewards in the ventral striatum. The response to rewards in prenatally exposed adolescents seemed to be hyposensitive. This might have implications for smoking initiation as well. The association between hyposensitivity and smoking initiation in adolescents was also shown by Peters *et al.* (2011). They showed hyposensitivity in the ventral striatum of adolescent ever-smokers (i.e. smoked at least one cigarette during the last 30 days) compared to their non-smoking peers (i.e. smoked never in their lives). There might also be a link to impulsivity, since these smokers were more impulsive in their behaviour measured via an intertemporal choice task. Further support for the possible link between ventral striatal hyposensitivity and substance use was found by Schneider *et al.* (2011). They showed a negative relation between risk-taking preference and the BOLD response in the ventral striatum of adolescents during the anticipation of rewards. Risk-taking preference as well as decreased BOLD in the ventral striatum was more pronounced in adolescents with potentially problematic substance use. Another study which corroborated the potential role of personality, including impulsivity, showed that personality, contributes more than behaviour (e.g. risk taking and risk adjustment) and reward-related brain activity to drinking initiation (Nees et al., 2012).

5.6 Conclusion and future perspective

The current thesis adds important results to the subject of individuals' behaviour in reward decision making, which is related to health-related behaviour and the underlying neural processes. Adolescent age as a risk factor and higher intelligence as a protective factor

regarding health-related behaviour were investigated. These risk and protective factors were linked to common neural processes in the brain and might extend the CNDS theory regarding these factors. Thus, the thesis contributes to the further understanding of how risk and protective factors act on health-related behaviour. Further, effects of acute and chronic nicotine intake on intertemporal choices have been shown. Moreover, the thesis leads to an integrative approach how age, intelligence and nicotine intake might interact on the behavioural and neural level and contribute to the transition to nicotine addiction.

Due to the limitations of our cross-sectional results, it is only possible to speculate about the course of development of reward decision making and the neural processes. Therefore, future studies should investigate development of reward decision making behaviour in a longitudinal design. Then it would be possible to test hypotheses about causal relationships. Specifically, it would be of interest in which way the development of behaviour and brain processing interacts with substance use. To achieve this, adolescent data presented in the current work were part of a longitudinal data collection. The second wave of data collection at age 16 has almost finished and the third wave at age 18 just started. Since many of the subjects did not start to drink or smoke at the time of their first participation in the study (at age 14) it will be possible to track development of substance use and related conditions. This will help to test the hypotheses which emerged from the current thesis. Specifically, it would be possible to test directly whether intelligence prevents addiction via a control network in the brain after a first smoking initiation during adolescence. Further, it could be tested whether the hyposensitivity in the ventral striatum is a pre-drug characteristic, which can discriminate between lifetime smokers, occasional smokers and non-smokers. Additionally, the role of consistency in substance use can be further investigated.

Beside these open questions to be addressed in the future, this thesis tested several variables and provides an integrative approach to explain possible mechanisms that influence health-related behaviour, especially in the context of addiction.

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7 Appendix

Supplementary material of studies 1, 2 and 3

7.1 Supplementary material study 1

Table S 1: Sample-sets of amounts and values (in brackets) for two subjects, one with an individual discount rate of k=0.0084 and another one with k=0.0025. In one case the immediate alternative amount was 10.00 Euro, in the other it was 7.00 Euro. The mean value of all rewards was 30.00 Euro for both subjects whereas the mean of all amounts was 49.55 Euro for subject 1 and 36.56 Euro for subject 2. All amounts and respective delays were shown in random order during the fMRI experiment.

10 days		**30 days**		**60 days**		**120 days**		**180 days**	
Sub 1	Sub 2	Sub 1	Sub 2	Sub 1	Sub 2	Sub 1	Sub 2	Sub 1	Sub 2
10.08 (9.30)	7.02 (6.84)	10.25 (8.19)	7.05 (6.55)	10.50 (6.98)	7.11 (6.16)	11.01 (5.48)	7.21 (5.52)	11.51 (4.58)	7.32 (5.02)
10.12 (9.34)	7.03 (6.85)	10.38 (8.29)	7.08 (6.58)	10.76 (7.15)	7.16 (6.21)	11.51 (5.73)	7.32 (5.61)	12.27 (4.88)	7.48 (5.13)
10.16 (9.38)	7.04 (6.86)	10.50 (8.39)	7.11 (6.60)	11.01 (7.32)	7.21 (6.26)	12.08 (5.98)	7.43 (5.69)	13.03 (5.19)	7.64 (5.24)
10.21 (9.49)	7.04 (6.86)	10.63 (8.49)	7.13 (6.63)	11.26 (7.49)	7.28 (6.30)	12.52 (6.23)	7.53 (5.77)	13.78 (5.48)	7.80 (5.35)
10.25 (9.46)	7.05 (6.87)	10.76 (8.59)	7.16 (6.65)	11.51 (7.65)	7.32 (6.35)	13.03 (6.49)	7.64 (5.85)	14.54 (5.79)	7.96 (5.46)
10.29 (9.50)	7.06 (6.88)	10.88 (8.69)	7.19 (6.68)	11.77 (7.82)	7.38 (6.40)	13.53 (6.73)	7.75 (5.93)	15.29 (6.09)	8.12 (5.57)
10.34 (9.53)	7.07 (6.87)	11.01 (8.79)	7.21 (6.70)	12.02 (7.99)	7.43 (6.44)	14.03 (6.99)	7.86 (6.02)	16.05 (6.39)	8.28 (5.68)
10.38 (9.57)	7.08 (6.90)	11.13 (8.89)	7.24 (6.73)	12.27 (8.16)	7.48 (6.49)	14.54 (7.24)	7.96 (6.10)	16.81 (6.69)	8.44 (5.79)
10.42 (9.61)	7.09 (6.91)	11.26 (8.99)	7.28 (6.75)	12.52 (8.32)	7.53 (6.54)	15.04 (7.49)	8.07 (6.18)	17.56 (6.99)	8.61 (5.90)
13.55 (12.50)	8.97 (8.75)	15.65 (12.50)	9.42 (8.75)	18.80 (12.50)	10.09 (8.75)	25.11 (12.50)	11.43 (8.75)	31.41 (12.50)	12.76 (8.75)
24.28 (22.39)	20.72 (20.20)	28.04 (22.39)	21.75 (20.20)	33.68 (22.39)	23.29 (20.20)	44.97 (22.39)	26.38 (20.20)	56.26 (22.39)	29.47 (20.20)
35.00 (32.29)	32.47 (31.66)	40.43 (32.29)	34.08 (31.66)	48.56 (32.29)	36.50 (31.66)	64.84 (32.29)	41.34 (31.66)	81.12 (32.29)	46.18 (31.66)
45.72 (42.18)	44.21 (43.11)	52.81 (42.18)	46.41 (43.11)	63.45 (42.18)	49.70 (43.11)	84.71 (42.18)	56.30 (43.11)	105.98 (42.18)	62.89 (43.11)
56.45 (52.07)	55.96 (54.57)	65.20 (52.07)	58.74 (54.58)	78.33 (52.07)	62.91 (54.57)	104.58 (52.07)	71.25 (54.57)	130.83 (52.07)	79.59 (54.57)
67.17 (61.97)	67.70 (66.02)	77.59 (61.97)	71.07 (66.02)	93.21 (61.97)	76.12 (66.02)	124.45 (61.97)	86.2 (66.02)	155.69 (61.97)	96.30 (66.02)
77.90 (71.86)	79.45 (77.48)	89.97 (71.86)	83.40 (77.48)	108.09 (71.86)	89.32 (77.48)	144.32 (71.86)	101.17 (77.48)	180.55 (71.86)	113.01 (77.48)
88.62 (81.75)	91.20 (88.93)	102.36 (81.75)	95.73 (88.93)	122.97 (81.75)	102.53 (88.93)	164.19 (81.75)	116.12 (88.93)	205.40 (81.75)	129.72 (88.93)
99.35 (91.64)	102.94 (100.39)	114.75 (91.64)	108.06 (100.39)	137.85 (91.64)	115.73 (100.39)	184.06 (91.64)	131.08 (100.39)	230.26 (91.64)	146.43 (100.39)

Table S 2: Subjective value related BOLD (Threshold t = 3.13; p = 10-3 and at least p<0.05, FDR-corrected in 25 contiguous voxels)

Anatomical area	**Hem.**	**Size**	**Coordinates**			**FDR corrected p-value**	**Z_{max}**
		(voxels)	**x**	**y**	**z**		
Ventral striatum, NAcc, Caudate	R	2765	9	9	-3	< 0.001	Inf
Ventral striatum, NAcc, Caudate	L		-9	6	-3	< 0.001	7.59
Anterior Cingulate	L		-3	51	0	< 0.001	7.38
Inferior Frontal Gyrus	L	269	-48	27	-3	< 0.001	5.12
Superior Frontal Gyrus	R	181	6	6	69	< 0.001	4.53
Superior Frontal Gyrus	L		-15	39	51	< 0.001	4.42
Superior Frontal Gyrus	L		-12	48	42	0.001	4.19
Precentral Gyrus	L	136	-39	-12	63	< 0.001	4.90
Precentral Gyrus	R	85	36	-15	66	< 0.001	4.46
Parietal Lobe: Supramarginal Gyrus	R	42	63	-45	27	< 0.001	4.35
Inferior Parietal Lobule	R		66	-39	33	0.002	3.68
Superior Temporal Gyrus	R	221	45	-30	-3	< 0.001	5.58
Superior Temporal Gyrus	L		-48	15	-9	< 0.001	4.87
Middle Temporal Gyrus	R		48	-18	-15	< 0.001	5.01
Middle Temporal Gyrus	L	64	-63	-33	-6	< 0.001	4.33
Inferior Temporal Gyrus	L		-60	-12	-21	0.004	3.46
Occipital Lobe: Lingual Gyrus	L	715	-9	-90	0	< 0.001	5.08
Occipital Lobe: Lingual Gyrus	R		9	-87	-3	< 0.001	4.88
Middle Occipital Gyrus	L		-21	-96	0	< 0.001	4.92

Table S 3: Subjective value related BOLD in adolescents (Threshold t = 3.13; p = 10-3 and at least p<0.05, FDR-corrected in 25 contiguous voxels)

Anatomical area	Hem.	Size (voxels)	Coordinates x	y	z	FDR corrected p-value	Z_{max}
Ventral striatum, NAcc, Caudate	L	1218	-9	6	-3	<0.001	Inf
Ventral striatum, NAcc, Caudate	R		9	6	-3	<0.001	Inf
Anterior Cingulate	L	1183	-6	39	-3	<0.001	7.33
Anterior Cingulate	L		-3	39	6	<0.001	7.03
Anterior Cingulate	R		9	39	9	<0.001	5.71
Superior Frontal Gyrus	R	35	3	6	69	0.001	3.93
Superior Frontal Gyrus	R/L		0	24	66	0.007	3.28
Cingulate Gyrus	R/L	198	0	-27	30	<0.001	5.02
Cingulate Gyrus	R/L		0	-18	33	<0.001	4.56
Precentral Gyrus	L	97	-39	-15	63	<0.001	5.08
Postcentral Gyrus	L		-45	-24	60	<0.001	4.40
Precentral Gyrus	R	31	39	-15	66	<0.001	4.22
Precentral Gyrus	R		51	-3	51	0.005	3.45
Parahippocampal Gyrus	L		-12	-6	-12	<0.001	7.12
Middle Temporal Gyrus	R	65	48	-30	-6	<0.001	4.68
Middle Temporal Gyrus	L	40	-60	-33	-9	0.003	3.67
Middle Temporal Gyrus	L		-57	-45	-12	0.004	3.51
Occipital Lobe: Cuneus	L	1018	-9	-93	0	<0.001	6.40
Occipital Lobe: Cuneus	R		24	-96	-6	<0.001	5.35
Occipital Lobe: Lingual Gyrus	L		-15	-78	-15	<0.001	5.16

Table S 4: Subjective value related BOLD in adults (Threshold t = 3.13; p = 10-3 and at least p<0.05, FDR-corrected in 25 contiguous voxels)

Anatomical area	**Hem.**	**Size**	**Coordinates**			**FDR corrected p-value**	**Z_{max}**
		(voxels)	**x**	**y**	**z**		
Anterior Cingulate	L	456	-3	51	0	< 0.001	5.62
Anterior Cingulate	R		3	33	-9	0.004	4.46
Ventral striatum, NAcc, Caudate	R	150	6	9	0	0.001	5.22
Ventral striatum, NAcc, Caudate	L		-6	6	3	0.006	4.19
Lentiform Nucleus	L	270	-30	-12	-6	0.006	4.15
Inferior Frontal Gyrus	L	61	-51	27	-6	0.007	4.07
Inferior Frontal Gyrus	R	118	48	30	-6	0.001	5.07
Superior Frontal Gyrus	L	51	-9	39	54	0.010	3.91
Middle Temporal Gyrus	R	95	48	-18	-15	0.003	4.51
Superior Temporal Gyrus	R		45	-30	-3	0.006	4.14
Parahippocampal Gyrus	R	63	30	-15	-12	0.001	4.81
Inferior Parietal Lobule	R		66	-33	36	0.010	3.91
Inferior Parietal Lobule	R		63	-36	24	0.018	3.56
Supramarginal Gyrus	R	79	63	-45	27	0.005	4.34

Table S 5: Areas where impulsivity (log k) is inversely correlated with reward value (based on median k) related BOLD response (Threshold t = 3.13; p = 10-3 and at least p<0.05, FDR-corrected in 25 contiguous voxels).

Anatomical area	**Hem.**	**Size**	**Coordinates**			**FDR cor-rected p-value**	**Z_{max}**
		(voxels)	**x**	**y**	**z**		
Thalamus	L/R	88	0	-12	9	0.007	4.47
Ventral striatum, Lentiform Nucleus	L		-15	0	6	0.009	3.6
Ventral striatum, Caudate	L		-12	0	15	0.009	3.46
Thalamus	R	28	18	-6	15	0.009	3.70
Ventral striatum, Lentiform Nucleus	R		12	0	3	0.009	3.61
Ventral striatum, Caudate	R		6	9	-3	0.012	3.22
Inferior Frontal Gyrus	R	32	54	27	6	0.009	3.78

Table S 6: Decision making related BOLD (Threshold t = 4.35; p = 10-5 and at least p<0.05, FDR-corrected in 25 contiguous voxels)

Anatomical area	**Hem.**	**Size**	**Coordinates**			**FDR corrected p-value**	**Z_{max}**
		(voxels)	**x**	**y**	**z**		
Occipital Lobe: Lingual Gyrus	L	26315	-12	-96	-6	< 0.001	Inf
Middle Occipital Gyrus	L		-24	-96	9	< 0.001	Inf
Middle Occipital Gyrus	R		39	-87	0	< 0.001	Inf
Inferior Occipital Gyrus	L		-42	-84	-9	< 0.001	Inf
Inferior Occipital Gyrus	R		45	-78	-12	< 0.001	Inf
Occipital Lobe: Lingual Gyrus	L		-18	-87	-12	< 0.001	Inf
Occipital Lobe: Cuneus	L		-27	-90	21	< 0.001	Inf
Occipital Lobe: Cuneus	R		18	-96	-6	< 0.001	Inf
Temporal Lobe: Fusiform Gyrus	L		-39	-75	-15	< 0.001	Inf
Temporal Lobe: Fusiform Gyrus	R		33	-78	-18	< 0.001	Inf
Superior Parietal Lobule (BA7)	L		-27	-63	48	< 0.001	Inf
Superior Parietal Lobule (BA7)	R		30	-63	48	< 0.001	Inf
Inferior Parietal Lobule (BA40)	L		-33	-51	45	< 0.001	Inf
Inferior Parietal Lobule (BA40)	R		45	-48	51	< 0.001	Inf
Parietal Lobe: Precuneus	R		30	-69	39	< 0.001	Inf
Cingulate Gyrus (BA23)	R		3	-30	27	< 0.001	Inf
Posterior Cingulate (BA30)	R		15	-66	6	< 0.001	Inf
Thalamus	L		-21	-30	-3	< 0.001	Inf
Cingulate Gyrus	L	47	-24	-48	24	< 0.001	-7.08
Thalamus	L		-15	-39	12	< 0.001	-5.01
Inferior Parietal Lobule	R	76	60	-30	33	< 0.001	-5.77
Anterior Cingulate	R	54	-3	18	-6	< 0.001	-5.77

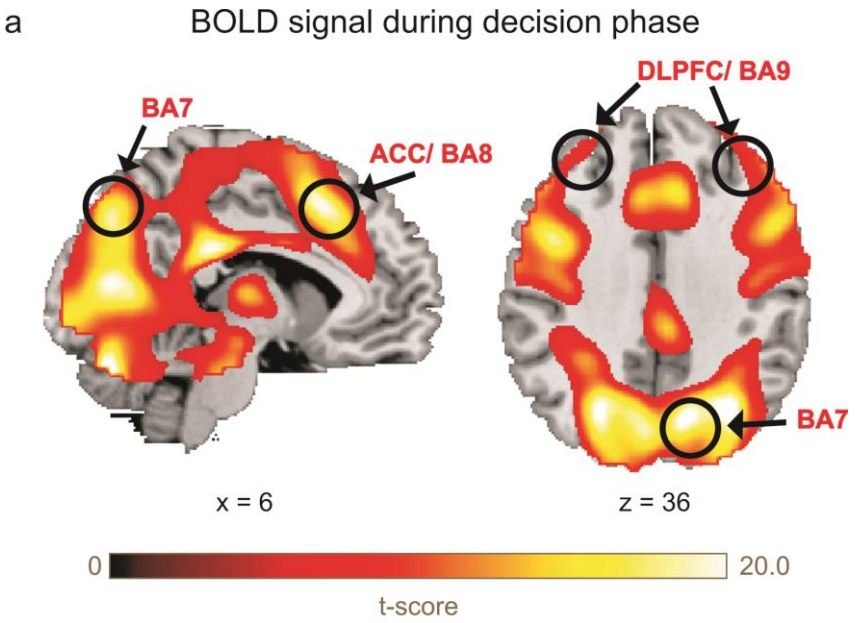
Table S 7: Decision making related BOLD in adolescents (Threshold t = 4.36; p = 10^{-5} and at least p<0.05, FDR-corrected in 25 contiguous voxels)

Anatomical area	**Hem.**	**Size**	**Coordinates**			**FDR corrected p-value**	**Z_{max}**
		(voxels)	**x**	**y**	**z**		
Occipital Lobe: Lingual Gyrus	L	28249	-12	-96	-6	< 0.001	Inf
Middle Occipital Gyrus	L		-36	-87	-6	< 0.001	Inf
Middle Occipital Gyrus	R		36	-87	-6	< 0.001	Inf
Inferior Occipital Gyrus	L		-39	-84	-9	< 0.001	Inf
Inferior Occipital Gyrus	R		45	-78	-12	< 0.001	Inf
Occipital Lobe: Cuneus	L		-24	-93	-3	< 0.001	Inf
Occipital Lobe: Cuneus	R		3	-75	12	< 0.001	Inf
Superior Parietal Lobule (BA7)	L		-24	-66	42	< 0.001	Inf
Superior Parietal Lobule (BA7)	R		30	-60	48	< 0.001	Inf
Parietal Lobe: Precuneus	R		30	-69	39	< 0.001	Inf
Cingulate Gyrus (BA23)	R		6	-30	27	< 0.001	Inf
Posterior Cingulate (BA30)	R		18	-63	6	< 0.001	Inf
Thalamus	L		-21	-27	-3	< 0.001	Inf
Thalamus	L/R	638	0	-30	12	< 0.001	- Inf
Caudate	R		18	-42	15	< 0.001	- Inf
Inferior Parietal Lobule	R	247	60	-30	33	< 0.001	- Inf
Supramarginal Gyrus	R		60	-57	27	< 0.001	- 5.52
Anterior Cingulate	L	175	-3	18	-6	< 0.001	- Inf
Parahippocampal Gyrus	R	32	36	-48	0	< 0.001	- 7.20
Transverse Temporal Gyrus	R		33	-39	9	< 0.001	- 4.55
Inferior Parietal Lobule	L	46	-60	-30	33	< 0.001	- 6.94

Table S 8: Decision making related BOLD in adults (Threshold t = 4.36; p = 10-5 and at least p<0.05, FDR-corrected in 25 contiguous voxels).

Anatomical area	**Hem.**	**Size**	**Coordinates**			**FDR cor-rected p-value**	**Z_{max}**
		(voxels)	**x**	**y**	**z**		
Middle Occipital Gyrus	L	14223	-24	-96	9	< 0.001	Inf
Occipital Lobe: Lingual Gyrus	L		-12	-96	-6	< 0.001	Inf
Superior Temporal Gyrus	R	48	48	-39	6	< 0.001	6.09
Superior Frontal Gyrus (BA9)	L	31	-33	48	33	< 0.001	5.29
Middle Frontal Gyrus (BA10)	L		-36	54	21	< 0.001	4.59

7.2 Supplementary material study 2



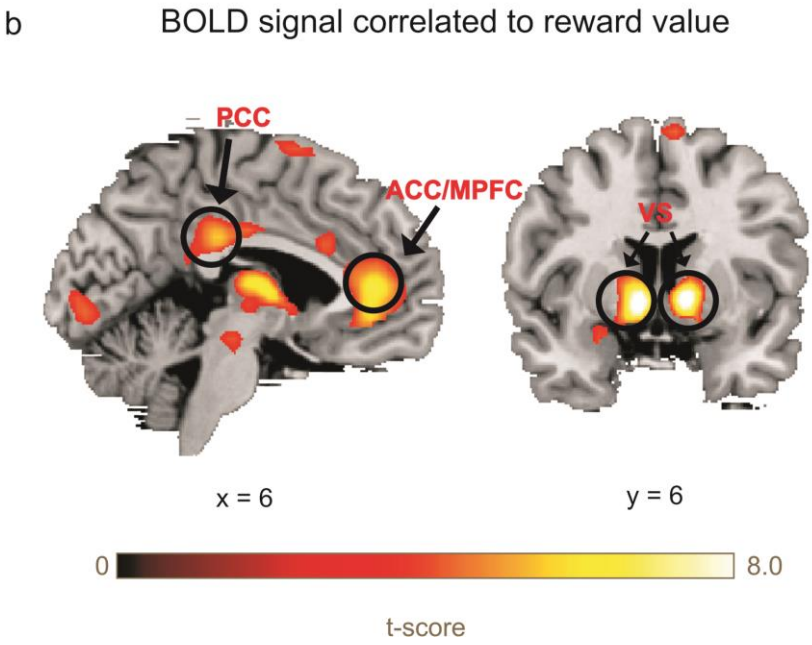


Figure S 1:BOLD main effecs of decision phase and reward processing: (a) BOLD signal during decision processing (threshold T = 4.89, p<0.05, FDR-corrected in 25 contiguous voxels). (b) BOLD signal correlated to value of the delayed reward (threshold T = 3.0, p<0.05, FDR-corrected in 25 contiguous voxels). ACC: anterior cingulate cortex, BA: Brodman area, DLPFC: dorsolateral prefrontal cortex, MPFC: medial prefrontal cortex, PCC: posterior cingulate cortex, VS: ventral striatum

7.3 Supplementary material study 3

Table S 9: Set of amounts and delays used for all participants.

Early € amount	Early time	Late € amount	Later time
20,56	4 weeks	23,64	6 weeks
15,65	immediate	23,48	4 weeks
35,35	2 weeks	36,41	4 weeks
16,32	4 weeks	20,40	6 weeks
7,66	4 weeks	7,89	6 weeks
19,21	2 weeks	19,40	4 weeks
15,35	4 weeks	20,72	6 weeks
10,96	2 weeks	13,71	4 weeks
22,89	4 weeks	24,03	6 weeks
25,53	2 weeks	26,29	6 weeks
15,71	4 weeks	17,28	6 weeks
14,54	immediate	16,72	2 weeks
11,53	immediate	14,42	2 weeks
20,36	2 weeks	27,48	4 weeks
18,80	immediate	19,74	4 weeks
24,85	immediate	28,58	4 weeks
23,71	4 weeks	35,56	6 weeks
25,35	2 weeks	25,61	6 weeks
16,69	immediate	16,86	2 weeks
7,99	immediate	8,23	4 weeks
26,63	immediate	39,95	2 weeks
19,35	immediate	21,28	4 weeks
11,46	immediate	11,57	4 weeks
6,53	2 weeks	7,18	4 weeks
17,54	immediate	23,67	2 weeks
21,33	2 weeks	23,46	6 weeks
14,05	immediate	17,56	4 weeks
19,21	2 weeks	25,94	6 weeks
30,18	2 weeks	37,73	6 weeks
13,72	2 weeks	20,59	4 weeks
18,5	immediate	24,98	4 weeks
17,96	2 weeks	18,86	6 weeks
24,98	immediate	26,23	2 weeks
9,75	4 weeks	9,85	6 weeks
13,18	2 weeks	19,78	6 weeks
34,88	immediate	38,37	2 weeks
13,94	2 weeks	14,63	4 weeks
35,93	2 weeks	41,32	6 weeks
24,69	2 weeks	28,40	4 weeks
11,56	Immediate	11,91	2 weeks

Table S 10: Repetition effects in non-smokers (session 1 vs. session 2): areas, where BOLD response differs between 1st and 2nd measure of the intertemporal choice task (nicotine and placebo are balanced between both measures; positive t values indicate higher BOLD at first measure; threshold t = 3.43, p = 10-3 in 20 contiguous voxels)

Region	**Side**	**Cluster Size (voxels)**	**MNI coordinates**			**T_{max}**
			x	**y**	**z**	
Decision epochs:						
Striatum, Lentiform nucleus, Putamen	R	266	8	-2	-12	4.77
			14	10	-10	4.43
Anterior Cingulate Gyrus	R	26	6	34	2	4.30
Superior Frontal Gyrus, BA8	L	37	-24	34	52	4.32
Frontal Lobe, BA6	R	20	6	10	72	3.99
Precuneus, BA19	L	25	-48	-74	38	4.61
Parietal Lobe, BA39	L		-42	-76	44	3.70
Thalamus	L/R	29	0	-8	12	4.57
Reward magnitude:						
Parahippocampal Gyrus, BA28	L	54	-18	-12	-10	-4.62
Brain stem	L/R	142	0	-30	4	-5.26
Delay to reward delivery:						
Inferior Frontal Gyrus BA9	L	62	-44	-4	24	4.67
Choice early:						
Inferior Frontal Gyrus, BA47	L	26	-22	32	-6	4.43
Precentral Gyrus, BA44	R	61	50	8	18	4.29
Precuneus, BA7	L	57	-24	-76	56	5.15
Medial Frontal Gyrus, BA10	R	24	6	46	-10	3.84
Middle Temporal Gyrus, BA38	R	46	34	4	-30	5.18
Temporal Lobe, BA20, BA21, BA22	R	105	44	-22	4	4.17
Temporal Lobe, BA21	L	53	-66	-48	6	3.81

7.3.1 Supplementary method

According to McClure *et al.*, (2004) we did an additional analysis where trials with one immediate option and trials with 2 delayed options where modelled separately.

7.3.2 Supplementary results

As to the beta areas (brain regions preferentially activated for choices in which money is available immediately), we could not replicate the effect reported by McClure *et al.*, (2004). In our sample, no region survived the threshold of 0,001, uncorrected. We therefore lowered the threshold to $p<0.05$ for explorative purposes. At this threshold we found several frontal brain regions (the medial frontal gyrus, the middle frontal gyrus, the superior frontal gyrus, the inferior frontal gyrus and the anterior cingulate gyrus), the middle temporal gyrus and regions within the parietal lobe (the Precuneus and the inferior parietal cortex), the right insula and the posterior cingulate gyrus (see suppl. Figure1a). In contrast to (McClure et al., 2004) there was no activation in the ventral striatum.

Regarding the delta areas (regions which are active while making choices independent of the delay), we replicated the results of McClure *et al.*, (2004). Beside regions found by McClure et al., (McClure et al., 2004) like the visual cortex, premotor and supplementary motor areas, the bilateral intraparietal cortex and right dorsolateral prefrontal cortex (DLPFC), right ventrolateral prefrontal cortex (VLPFC), and right lateral orbitofrontal cortex (LOFC), we additionally found contra-lateral activations in the same regions and activations in the anterior and posterior cingulate gyrus.

There were no group differences between smokers and non-smokers as well as between smokers under placebo and under nicotine regarding the contrast between immediate option trials and trials without an immediate option. All differences between groups found during the decision epochs of all trials (delta regions) were reported in the results section of the main document.

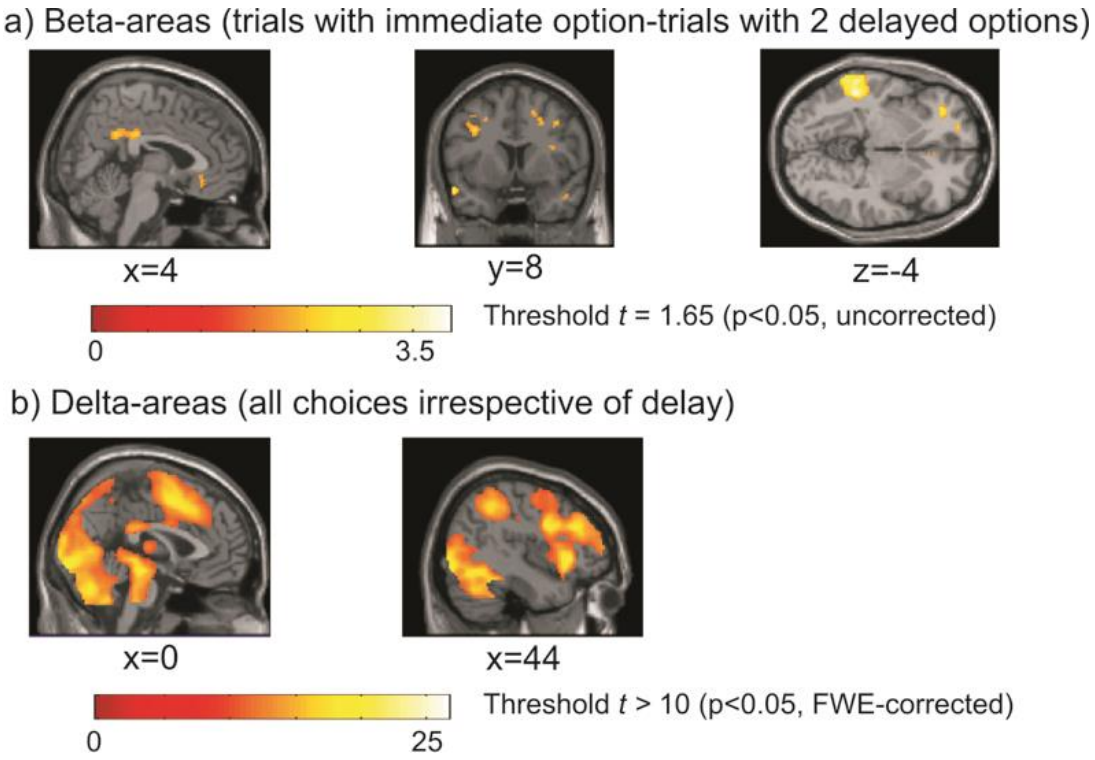


Figure S 2: Result figure according to the analysis of McClure et al, 2004; (a) Beta areas; for explorative analysis trials with an immediate option were contrasted to trials with only delayed options at a threshold of T(84)=1.65 (p<0.05, uncorrected) in 20 contiguous voxels. (b) Delta areas; all choices are displayed at a threshold of T(84)>10 (p<0.05, FWE-corrected) in 20 contiguous voxels.

Statement

Die Arbeit wurde an der Professur für Systemische Neurowissenschaften der Medizinischen Fakultät Carl Gustav Carus der Technischen Universität Dresden unter wissenschaftlicher Betreuung von Prof. Dr. med. Michael Smolka angefertigt. Es haben keine früheren erfolglosen Promotionsverfahren stattgefunden. Die Promotionsordnung der Fakultät Mathematik und Naturwissenschaften der Technischen Universität Dresden vom 23. Februar 2011 erkenne ich an.

Versicherung

Hiermit versichere ich, dass ich die vorliegende Arbeit ohne unzulässige Hilfe Dritter und ohne Benutzung anderer als der angegebenen Hilfsmittel angefertigt habe; die aus fremden Quellen direkt oder indirekt übernommenen Gedanken sind als solche kenntlich gemacht. Die Arbeit wurde bisher weder im Inland noch im Ausland in gleicher oder ähnlicher Form einer anderen Prüfungsbehörde vorgelegt.

Dresden, 13.03.2013

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Stephan Ripke