Why teens take risks ... : a neurocognitive analysis of developmental changes and individual differences in decision-making under risk

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What motivates the adolescent? Brain regions mediating reward sensitivity across adolescence

The relation between brain development across adolescence and adolescent risky behavior has attracted increasing interest in recent years. It has been proposed that adolescents are hypersensitive to reward because of an imbalance in the developmental pattern followed by the striatum and prefrontal cortex. To date it is unclear if adolescents engage in risky behavior because they overestimate potential rewards or because they respond more to received rewards and whether these effects occur in the absence of decisions. In this study, we used an fMRI paradigm that allowed us to dissociate effects of the anticipation, receipt and omission of reward in 10-12, 14-15, and 18-23 year-old participants. We show that in anticipation of uncertain outcomes the anterior insula is more active in adolescents compared to young adults, and that the ventral striatum shows a reward related peak in middle adolescence, whereas young adults show orbitofrontal cortex activation to omitted reward. These regions show distinct developmental trajectories. This study supports the hypothesis that adolescents are hypersensitive to reward, and adds to the current literature in demonstrating that neural activation differs in adolescents even for small rewards in the absence of choice. These findings may have important implications for understanding adolescent risk-taking behavior.

3.1 Introduction

Often decisions are made in uncertain situations, in which not all the information needed to make a rational decision is known. When choices in uncertain situations are associated with possible negative outcomes, they are considered risky. An increase in risky behavior is one of the most salient characteristics of adolescence (Arnett 1999; Boyer 2006; Steinberg 2004). This change in behavior suggests a difference in the decision making processes of adolescents compared to adults. That is, adolescents may choose differently between competing courses of action in an uncertain situation, because they weigh the possible outcomes and the probabilities with which these occur differently compared to adults. Prior studies have suggested that adolescents are biased towards taking risks because of differences in the way they experience rewards (Bjork et al. 2004; Ernst et al. 2005; Galvan et al. 2006; May et al. 2004; Van Leijenhorst et al. 2006).

Functional magnetic resonance imaging (fMRI) studies have identified brain regions related to outcome anticipation and processing. Many studies have shown that the ventral striatum responds to anticipation of potential rewards (Breiter et al. 2001; Dagher 2007; Knutson et al. 2001; Tom et al. 2007), which was confirmed by a recent meta analysis (Knutson and Greer, 2008). In addition, the anterior insula have been implicated in the anticipation of outcomes, activation in this region is also often associated with the uncertainty associated with anticipation (Critchley et al. 2001; Volz et al. 2003). Finally, several studies in adults have shown that medial prefrontal, orbitofrontal and anterior cingulate cortex are involved in processing rewards (Bechara 2001; Knutson et al. 2001; O'Doherty et al. 2001; O'Doherty et al. 2002; Rolls 2000).

The functional development of these regions is not well understood. The few developmental studies to date show a seemingly inconsistent pattern of results. Adolescent risk-taking has on the one hand been associated with a *decreased* sensitivity of the ventral striatum to reward in adolescents compared to adults. This neural response has been suggested to lead adolescents to seek more stimulating experiences in order to compensate for low levels of activation in the ventral striatum (Bjork et al. 2004; Spear 2000). On the other hand, adolescent risk-taking has been associated with an *increased* responsiveness of the ventral striatum to reward (Galvan et al. 2006). In these studies, it was suggested that this increase in the response to potential rewards in

combination with immature cognitive control abilities (resulting from the protracted development of the prefrontal cortex (PFC)) biases adolescents towards taking risks (Casey et al. 2008b; Ernst et al. 2006; Galvan et al. 2006).

The interpretation of these developmental findings is complicated for two reasons. First, there is a large variance in the ages of participants that have been included in these studies on adolescent reward processing. This is problematic because adolescents form a very heterogeneous group, for instance, in early adolescence developmental changes could be influenced by pubertal changes. In prior studies adolescents from a broad age range have been included. For example, in the study by (Bjork et al. 2004), the adolescent group consisted of participants aged 12-17-years, which may hinder our interpretation of the pattern of developmental change. Structural brain imaging studies have demonstrated that development of brain structure in terms of grey and white matter proportion continues throughout adolescence (Giedd et al. 1999; Gogtay et al. 2004), and a recent study has shown that these developmental changes follow a nonlinear pattern in many brain regions (Shaw et al. 2008). A second difficulty is that different experimental paradigms have been used in prior reports, making it difficult to compare results. For example, in prior studies rewards were dependent upon participants' task performance, and the requirements for obtaining rewards varied. Rewards could depend on reaction times (e.g. (Bjork et al. 2004), or on response accuracy/ probability matching (e.g. (Ernst et al. 2005; Eshel et al. 2007; Galvan et al. 2006; Van Leijenhorst et al. 2006). In addition, reward magnitude (Bjork et al. 2004; Galvan et al. 2006) reward probability (May et al. 2004; Van Leijenhorst et al. 2006) or both magnitude and probability (Ernst et al. 2005; Eshel et al. 2007) were manipulated. It is therefore difficult to relate developmental differences in ventral striatum activation to risk taking, or reward processing more generally. Recently, studies on adult decision-making have attempted to predict behavior based on preceding changes in activation of the ventral striatum (Knutson et al. 2008a). These studies showed that increased ventral striatum activation is associated with an increased willingness to take risks in adults. In a prior study including adults, Knutson et al. (2008b) used a decision-making task, and presented rewarding pictures that were unrelated to the task. Presentation of these pictures was related to increased activation of the ventral striatum and to increased willingness to take risks (Knutson *et al*. 2008b). Thus, if a peak in activation of the ventral striatum in

adolescents drives them to take risks, it is important to understand the extent to which this region is independent of behavioral requirements. In addition, it is important to understand at what phase, during the anticipation or processing of rewards, differences between adolescents and adults are observed. A better understanding of the causes of adolescent reward processing can help interpret the potentially harmful risky behavior that many adolescents engage in. It is important to understand whether adolescents are more likely to engage in risky behavior compared to adults because they overestimate potential rewards (in an early phase of the decision-making process), or because their response to received rewards differs from that of adults (in a later phase). Insight into these possible differences in reward sensitivity in adolescence informs us about the processes that underlie adolescent real-world risky behavior. In addition this knowledge could aid attempts to intervene and protect adolescents against the problems they face. Basic differences in reward related brain regions between participants form different ages may complicate the interpretation of developmental changes in behavior. One way to work around this difficulty is to study reward processing using an experimental task in which reward and risk are unrelated to participants' behavior (see Tobler et al. 2008) for a similar approach). Therefore, the goal of this study was to examine developmental differences in neural activation related to different phases of reward processing in the absence of behavior.

We compared the neural substrates of outcome anticipation and outcome processing in early and middle adolescence and young adulthood using fMRI. In order to identify the pattern of development of brain regions implicated in the processing of reward we included three homogenous age groups (10-12 year olds, 14-15 year olds and 18-23 year olds). These participants performed a Slot Machine Task (Donkers et al. 2005), a simple paradigm in which small monetary rewards are unpredictable and unrelated to behavior. In this task, participants view three slot machines in which pictures of fruit are presented consecutively. Only when these three pictures are the same, participants win money. The task involves the presentation of three different conditions: 1) all three pictures are different (referred to as the XYZ conditions), 2) the first two pictures are the same but the third is different (referred to as the XXY conditions) and 3) all three pictures are the same (referred to as XXX conditions). In this way, the paradigm allowed us to dissociate brain activation associated with outcome anticipation (when the first two out of three pictures are the same versus

all three pictures are different; XXY vs XYZ), processing of reward (when all three pictures are the same versus the first two out of three pictures are the same; XXX vs XXY), and omission of reward (XXY vs XXX).

Our analyses focused on identifying brain regions implicated in reward processing and uncertainty, including the striatum, the insula and the orbitofrontal cortex (OFC). Our first hypothesis was that these regions show functional development which is reflected in a different pattern of activation in the different age groups. We tested for linear and nonlinear developmental patterns. Our second hypothesis was that if adolescent risk taking is associated with increased sensitivity to reward this should be reflected in a peak in activation in the ventral striatum in this age group. We examined at which stage, during anticipation or processing of outcomes, the ventral striatum would show different responses in the absence of behavioral requirements, and whether the response to rewards in this region would be increased or decreased in adolescents compared to adults. The results are expected to provide insight in the development of reward related brain regions during adolescence, and contribute to the interpretation of differences in neural responses between adolescents and adults in more complex reward and risk-taking tasks.

3.2 Method

3.2.1 Participants

Fifty-three healthy, right-handed volunteers participated in the study, fifteen 18-23 year olds (7 females; mean age = 20.2, SD = 1.6), eighteen 14-15 year olds (10 females; mean age = 15.0, SD = 0.7), and seventeen 10-12 year olds (8 females; mean age 11.6, SD = 0.8). Informed consent was obtained from all participants and from a primary caregiver in case participants were younger than 18 years of age. The study was approved by the Medical Ethical Committee at the Leiden University Medical Centre. Data from three additional adult participants were excluded because of technical difficulties. Data for participants who had moved more than 3 mm in any direction were excluded from the analyses. For this reason, the data of three participants (a 14, 15 and 10 year old) were excluded. Average movement was .52 mm for the 18-23 year olds, .68 mm for the 14-15 year olds, and .62 mm for the 10-12 year olds. The

difference in average movement between the age groups was not significant ($p > .1$).

3.2.2 Behavioral assessment

Prior to scanning, all participants were prepared for the scan session in a quiet laboratory in which a mock scanner was present. This mock scanner, which simulated the environment and sounds of an actual MRI scanner, gave minors the opportunity to become accustomed to the scanner environment, and was used to explain the scanning procedure to all participants. In order tot obtain an estimate of IQ, age appropriate versions of two subtests of the Wechsler Adult Intelligence Scale (Wechsler 1981) or the Wechsler Intelligence Scales for Children (Wechsler 1991) - Similarities and Block Design - were administered to all participants. For 10-12 year olds, 14-15 year olds and 18-23 year olds estimate IQs were 119.7 (SD = 9.7), 106.0 (SD = 9.0) and 108.7 (SD = 9.4) respectively. 10-12 year olds' average IQ was significantly higher relative to the other two age groups ($F(2, 49) = 11.62$, $p = .001$) but overall participants' IQs fell in the average range. The analyses reported below were all corrected for differences in IQ by adding IQ as a covariate factor to the analyses. However, none of the effects were influenced by IQ differences. Therefore, IQ differences are not described further.

All participants were screened for psychiatric conditions, drug use, head injuries and contraindications for MRI using a checklist. No participants reported any problems. In addition, participants in the two youngest age groups were screened for behavioral problems using parent-ratings on the Child Behavior Checklist (Achenbach 1991). Scores for all participants fell within the non clinical range.

3.2.3 Experimental Design

Participants performed the Slot Machine Task, a child-friendly version of a paradigm used previously by (Donkers et al. 2005). Each trial started with the presentation of three empty slot machines. After 500 ms, a coin was presented at the bottom of the screen for 1000 ms, which served as a cue. In order to keep participants engaged in the (otherwise passive) task, they were instructed to start the machines by pressing a pre-specified button with their right index finger on presentation of the cue. The response had to be given within a 1000 ms time window.

Following the 1000 ms response window, three pictures, each one of three possible fruit types – a kiwi, a pear or a pair of cherries - were presented consecutively, from left to right in the slot machines, every 1500 ms (See Figure 3.1).

Pictures were presented in three possible orders: 1) three different pictures (e.g., kiwi-pear-cherries, referred to as XYZ trials), 2) two identical and one different picture (e.g., kiwi-kiwi-cherries, referred to as XXY trials) or 3) three identical pictures (e.g., kiwi-kiwi-kiwi, referred to as XXX conditions). These three trial types represent three experimental conditions. The order in which trials were presented was randomized and participants were presented with a new combination of the three pictures on each trial. Participants were instructed in advance that they would gain € 0.05 on each XXX trial, and that they would not gain money on the other types of trials. When participants failed to respond during the 1000 ms. cue presentation, the trial ended and they received a € 0.10 penalty. This occurred on less than 5% of the trials. At the end of the experiment the total winnings (€ 1.50) were added to the amount that participants received as reimbursement for participating in the study.

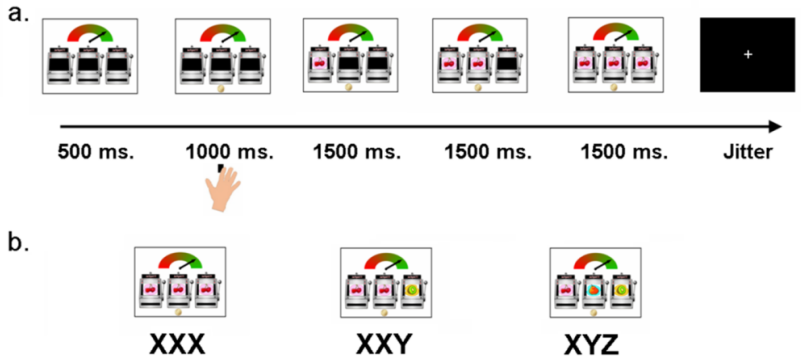

Figure 3.1 *Example of a.) a trial, b.) a possible outcome displays for the Slot Machine Task. Following a 1000 ms. time window in which participants could respond to the cue, three pictures appeared consecutively every 1500 ms. resulting in three trial types: XXX, XXY or XYZ. Participants won € 0.05 on each XXX trial, and did not win in the other conditions.*

3.2.4 MRI Data Acquisition

Trials were presented over the course of two event-related scans that each lasted approximately 7 minutes. The visual stimuli were projected

onto a screen that participants could see via a mirror attached to the head coil. During scanning participants were presented with a total of 120 trials, in which XXX, XXY and XYZ trials were intermixed, such that 60 XYZ trials, 30 XXY and 30 XXX trials were presented in total, with 60 trials in each run. Age related differences in response to rewards could be influenced by slow maturation of the ability to learn probabilities and predict risk. We controlled for this possibility by presenting the three consecutive stimuli in pseudo-random order to maximize uncertainty. On all trials after presentation of the first picture the probability that the next picture in the series of three was the same was always 50%. In the same way, after two identical pictures had been presented the probability that the third picture was the same was 50%. (50% XYZ, 25% XXY, 25% XXX trials, following (Donkers et al. 2005). Periods of fixation lasting between 1 and 3 s, jittered in increments of 500 ms, were added in between the experimental trials.

Scanning was performed using a standard whole-head coil on a 3 Tesla Philips scanner at the Leiden University Medical Center (LUMC). Functional data were acquired using a T2*-weighted gradient-echo echo-planar pulse sequence (38 contiguous 2.75 mm oblique axial slices, using interleaved acquisition, TR = 2.211 s, TE = 30 ms, 2.75 x 2.75 mm inplane resolution, 230 volumes per run). The first two volumes of each scan were discarded to allow for T1-equilibration effects. High-resolution T2* weighed images and high resolution T1 anatomical images were collected at the end of the scan session. Head motion was restricted using a pillow and foam inserts that surrounded the head.

3.2.5 fMRI preprocessing and Statistical analysis

Data pre-processing and analysis was conducted using SPM2 (Wellcome Department of Cognitive Neurology). Images were corrected for differences in timing of slice acquisition, followed by rigid body motion correction. Structural and functional volumes were spatially normalized to T_1 and echo planar imaging templates, respectively. The normalization algorithm used a 12-parameter affine transformation together with a nonlinear transformation involving cosine basis functions. During normalization the data was resampled to 3-mm cubic voxels. Templates were based on the MNI305 stereotaxic space (Cocosco et al. 1997). Functional volumes were smoothed with an

8-mm full-with at half maximum isotropic Gaussian kernel. Statistical analyses were performed on individual subjects' data using the GLM in SPM2. The fMRI time series were modeled as a series of events convolved with a canonical hemodynamic response function (HRF) in two separate models. We modeled each trial in the three different conditions (XXX, XXY, and XYZ) as a zero duration event around the onset times of the second stimulus in a first model, and around the onset times of the third stimulus in a second model. Error trials, defined as those trials where the participant did not respond within the 1000 ms cue window, were modeled separately and were excluded from the fMRI analyses.

For each participant the parameter estimates of height of the best-fitting canonical HRF for each condition were used in pair wise contrasts. For the first model we computed contrast images for the comparison of XXY and XYZ (i.e. comparing the situation where participants had first seen two pictures that were the same (XX) versus two pictures that were different (XY)); which revealed brain activation patterns related to the *anticipation* of the outcome of trials, based on the hypothesis that adolescents are more sensitive to potential rewards than adults. For the second model we computed contrast images for the comparison of XXX and XXY conditions; comparing brain activation patterns related to the processing of the outcome of trials. The resulting contrast images computed for each participant were submitted to second level group analyses. At the group level, whole brain contrasts between conditions were computed by performing one-tailed t-tests on these images, treating participants as random effect. Whole brain statistical maps were thresholded at $p < .001$, with an extent threshold of 5 contiguous voxels.

3.2.6 Statistical Analyses: Age related differences

Since we were especially interested in the pattern of activation related to outcome anticipation and outcome processing in the three different age groups, we performed voxelwise ANOVAs to identify regions that showed age-related differences in activation. We tested for linear (-1 0 1), quadratic (-0,5 1 -0,5) and curvilinear (1 -0,5 -0,5), (-0,5 -0,5 1) effects in the in the contrasts of XXY - XYZ for the first model (outcome anticipation), and XXX - XXY for the second model (outcome processing). ANOVAs were considered significant at a

statistical threshold of .001 uncorrected for multiple comparisons, with an extent threshold of 5 contiguous voxels.

3.2.7 Imaging Results: Region of Interest Analysis

We used the MARSBAR toolbox for use with SPM2 (Brett et al. 2002) to perform region of Interest (ROI) analyses to further characterize patterns of activation. We created 6 mm spherical ROIs centered at the peak activity voxel in the regions that were identified in the ANOVAs testing for age related differences. In addition we used MARSBAR to extract BOLD activity time series in these ROIs by averaging the time courses for the different experimental conditions starting at the onset of each trial. These time courses are displayed for illustrative purposes in Figures 3.2 and 3.3.

3.3 Results

3.3.1 Outcome Anticipation

We conducted a GLM analysis on the functional data modeled at the onset of the second stimulus, and computed the voxelwise contrast of XXY > XYZ for 10-12-year-olds, 14-15-year-olds and 18-23-year-olds separately. These analyses resulted in largely overlapping areas of activation for the three age groups. In all age groups, outcome anticipation was consistently associated with activation in the right anterior insula (see Figure 3.2 top panel). For 10-12 year olds and 14-15 year olds anterior insula activation was found in both hemispheres. In addition, the adolescent age groups showed activation clusters in the ventral striatum and dorsal cingulate cortex. Significant clusters and corresponding MNI coordinates are reported in Supplemental Table 3.1.

The voxelwise ANOVAs testing for age related changes for the XXY - XYZ contrast did not result in any significant clusters at a threshold of $p < .001$. At a more liberal threshold ($p < .005$) the ANOVA testing for the -1 0 1 contrast revealed a linear change in activation with age in the right anterior insula (peak at: 42, 12, -3, z = 2.95), F (1, 47) = 11.24, $p = .002$. We created a 6 mm spherical ROI centered at this voxel and performed an Age group (3) x Condition (2) ANOVA on the data extracted from this ROI to further characterize activation patterns in this

region. Average time series for this ROI are plotted in the bottom panel of Figure 3.2. The ANOVA for this ROI resulted in an Age group x Condition interaction, F (2, 47) = 7.00, p =.002. Follow up comparisons confirmed that this region was more active in the XXY compared to the XYZ condition in the 10-12-year-olds F (1, 16) = 11.26, p = .004, and 14-15-year-olds F (1, 17) = 3.62, p = .005. For the 18-23 year olds the difference between conditions was not significant (p = .19).

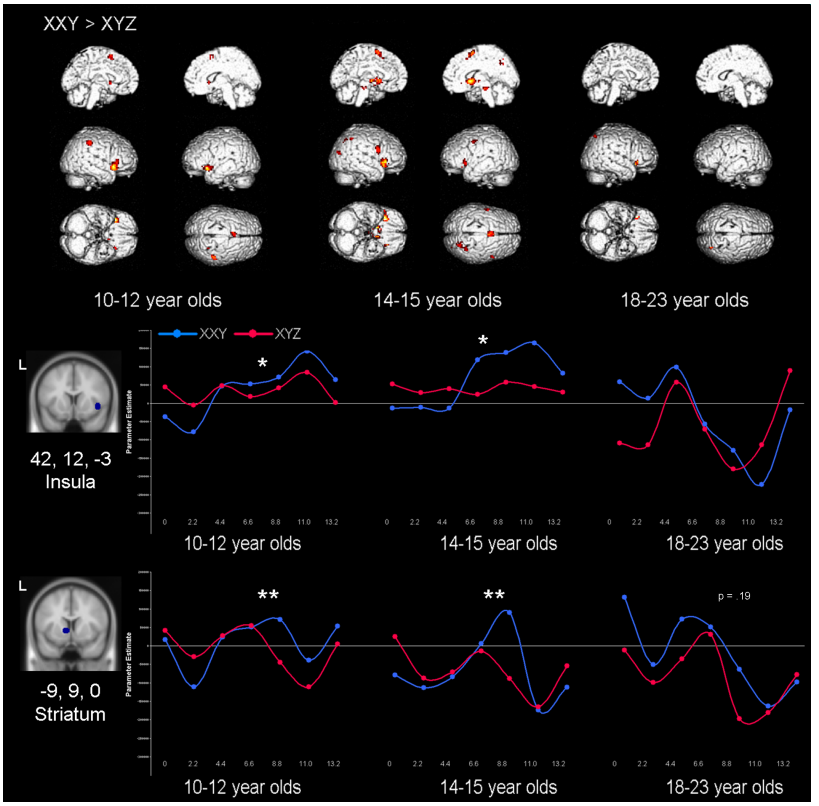

Figure 3.2 *Whole brain results for the 10-12 –year-old, 14-15-year-old and 18-23-year-old participants related to the anticipation of possible reward for the contrast of XXY > XYZ at a p < .001 uncorrected threshold (top panel). And 6 mm spherical ROIs and average time courses for the three age groups for the anterior insula, and striatum (lower panel).*

No age related changes for the XXY - XYZ contrast were found in the striatum. An ANOVA did reveal that this region was active in all age groups (peak at: -9, 9, 0, z = 4.57) in anticipation of outcomes, F (3, 47) = 13.11, p < .001. As anticipated, ANOVAs on the data extracted from the 6 mm spherical ROI for this region resulted in a main effect of

Condition, F (1, 47) = 23.73, p < .001, and no significant interaction with Age Group (p = .1). These results demonstrate that the striatum was more active in anticipation of potential reward to the same extent in all age groups. Nevertheless, comparisons for the age groups separately suggest a larger ventral striatum response in the adolescent groups. That is, in the 10-12 and 14-15 year-olds the XXY condition resulted in significantly more activation compared to the XYZ condition (p's for the main effect of Condition = .001), whereas in adults this difference only showed a trend towards significance (p = .09).

3.3.2 Outcome Processing

To examine brain activation patterns related to the processing of outcomes, a similar GLM analysis was performed on the functional data modeled at the onset of the third stimulus. Again, we computed the contrasts of interest for 10-12-year-olds, 14-15-year-olds and 18-23-year-olds separately. For the contrast of XXX > XXY (reward processing) we found activation in the striatum and dorsal cingulate cortex for 10-12-year-olds and 14-15-year-olds (see Figure 3.3 top panel). No significant clusters were found for the 18-23-year-olds, not even at a more liberal uncorrected threshold of p < .005. 14-15-year-olds also showed activation in left lateral prefrontal cortex.

A GLM for the reverse contrast of XXY > XXX (processing of omitted reward) did not reveal any significant clusters for both the 10-12-year-olds and 14-15-year-olds. In contrast, a region in the left OFC was found to be more responsive to omitted rewards in 18-23-year-olds at an uncorrected threshold of p < .001. An overview of significant clusters and corresponding MNI coordinates are reported in Supplemental Table 3.2.

The voxelwise ANOVAs testing for age related changes for the XXX - XXY contrast confirmed the whole brain findings for the XXX > XXY contrast by showing that activation in the striatum differed between adolescents and young adults. At an uncorrected threshold of p < .001 the ANOVA testing for the -0.5 1 -0.5 contrast revealed a cluster in the ventral striatum (peak at 12, 9, -15, z = 3.68) that showed a quadratic developmental pattern, F (1, 47) = 17.64, p < .001. The Age group (3) x Condition (2) ANOVA on the data extracted from the 6 mm spherical ROI centered at this voxel revealed that his region was more active in the XXX compared to the XXY condition in 14-15-year-olds F (1, 17) =

22.84, $p < .001$, but did not differ between conditions in the 10-12-year-olds ($p = .41$) and 18-23-year-olds ($p = .12$) (see Figure 3.3 bottom panel). The whole brain contrasts for the separate age groups revealed a region in the lateral OFC which was responsive to omitted rewards in the adult group. This finding was confirmed with an ANOVA testing for a curvilinear developmental trend with the -0.5 -0.5 1 contrast that resulted in a region in lateral OFC (peak at: -27, 48, -3, z = 3.05), F (1, 47) = 11.99 $p = .001$ (see Figure 3.3 bottom panel). ANOVAs on the 6 mm spherical ROI for this region resulted in a Condition x Age group interaction F (2, 47) = 8.67, $p = .001$. Follow up comparisons confirmed that this region only showed an increased response to the omission of rewards compared to received rewards in the 18-23-year-olds F (1, 14) = 7.38, $p = .02$.

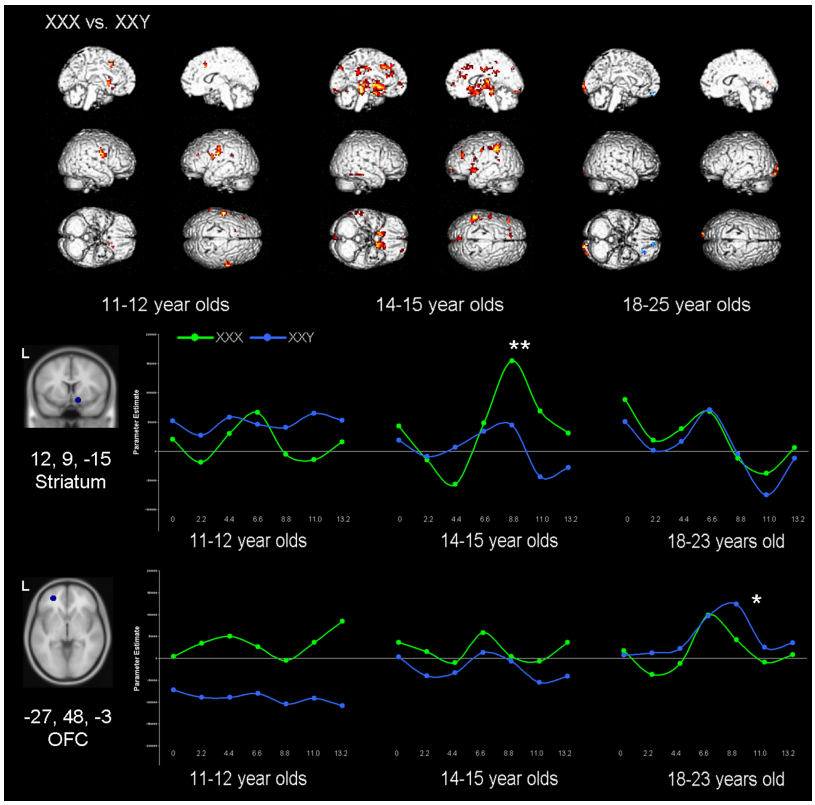

Figure 3.3 *Whole brain results for the 10-12 –year-old, 14-15-year-old and 18-23-year-old participants related to the anticipation of possible reward for the contrast of XXX > XXY at a p < .001 uncorrected threshold (top panel) and XXY > XXX (in blue). And 6 mm spherical ROIs and average time courses for the three age groups for the striatum and OFC (lower panel).*

3.4 Discussion

This study was motivated by the question how adolescents differ from adults in their sensitivity to uncertain reward. We examined the developmental trajectory of brain activation related to the processing of uncertain reward during the anticipation and outcome phases. Prior studies have reported inconsistent findings on adolescent reward processing, showing both *over*active (Galvan et al. 2006) and *under*active (Bjork et al. 2004) incentive-related neurocircuitry in adolescence. The present study differed from these previous studies in that we used a paradigm which resulted in probabilistic reward that was not dependent on behavior. This approach allowed us to examine basic differences in reward sensitivity under uncertainty. In addition, we examined neural differences in three distinct age groups; 10-12-year-olds, 14-15-year-olds, and 18-23-year-olds, which enabled us to test for different patterns of age related change.

The study yielded two main results: 1) when anticipating uncertain rewards, all age groups showed increased activation in the striatum, but a cluster in the anterior insula showed a linear decrease in activation form early adolescence to adulthood. 2) When processing the outcome of trials, middle adolescents were more responsive to received rewards as indicated by increased activation in the ventral striatum, whereas young adults responded most to the omission of rewards as indicated by increased activation in the OFC. In general, our findings support the hypothesis that middle adolescence is characterized by overactive incentive-related neurocircuitry, but we show that this effect is most pronounced during the phase of reward receipt. In light of the results of prior studies these results favor the hypothesis that overactive reward related circuitry and immature PFC circuitry potentially bias adolescents towards taking risks (see also (Casey et al. 2008a; Ernst et al. 2005; Galvan et al. 2006).

3.4.1 Developmental changes in outcome anticipation

Anticipation of outcomes was associated with activation in the striatum and anterior insula when the first two stimuli were identical, and indicated the possibility of winning. Activation in the insula showed a linear decrease with age; this region was most active in 10-12 year olds, less active in 14-15 year olds, and least active in 18-23 year olds when anticipating reward. In the paradigm that we used, the anticipation of

potential reward was associated with maximum uncertainty. After presentation of two of the same pictures, the probability of the third picture being the same or different was equal. In contrast, when the second picture was different from the first, a reward was no longer possible, and as a consequence there was no uncertainty associated with the anticipation of the outcome. The age related change in anterior insula activation could therefore reflect differences in at least two processes: 1) positive arousal associated with the anticipation of receiving a reward, or 2) the uncertainty when anticipating an unknown outcome.

Our results are consistent with the results of recent studies which have implicated the anterior insula in situations where decisions are associated with uncertainty (Huettel 2006; Huettel et al. 2005; Paulus et al. 2003; Volz et al. 2003; Volz and von Cramon 2006). The anterior insula have often been implicated in the experience of psychophysiological arousal. It has been suggested that the insula aid decision making by reflecting the autonomic nervous system responses to risk associated with a decision (Bechara 2001; Critchley et al. 2001; Paulus et al. 2003). Large autonomic signals preceding a disadvantageous decision have been suggested to serve as a warning signal that protect against risk-taking (Bechara et al. 1997). In light of this hypothesis the increased insula response in younger adolescents seems contradictory. However, other studies have suggested that this autonomic signal reflects the salience of the decision that has to be made (Tomb et al. 2002), and prior developmental studies showed that children experience autonomic signals when anticipating risky decisions, but fail to use these signals to optimize their decisions (Crone et al. 2005; Crone & Van der Molen 2004, 2007). In the current study, the increased insula activation in young adolescents could reflect immaturity of this region. The youngest participants could have experienced increased psychophysiological arousal related to the uncertainty associated with anticipation of a possible reward. Even though we did not collect subjective ratings of affect, previous studies have attempted to correlate experienced affect and patterns of brain activation. A recent study found that while activation in the ventral striatum correlated with reported positive affect, activation in the anterior insula correlated with both positive and negative reported affect (Samanez-Larkin et al. 2007). The results from this study suggest that the anterior insula might contribute to decision-making by reflecting general arousal in uncertain situations.

Huettel (2006) dissociated uncertainty related to the amount of potential reward that could be gained (reward risk), and uncertainty with regard to the optimal response (behavioral risk). He showed that activation in the anterior insula was selectively influenced by uncertainty related to response selection. Our results add to this finding by showing that the anterior insula is involved in uncertain situations in the absence of response selection, suggesting that this region may have a more general role in representing uncertainty of outcomes. A recent study (Preuschoff et al. 2008), showed that the anterior insula reflect the degree of uncertainty in a way similar to that in which the striatum is sensitive to the magnitude of reward. The authors suggest that the anterior insula could support processes similar to the reward prediction errors in the striatum. The linear decrease in activation in this region shows that anterior insula function is immature in adolescence, and could be taken to suggest a greater difficulty in adolescents to estimate the risk involved in an uncertain situation. Possibly, adolescents expected reward more often compared to adults in the present study because they did not learn that the occurrence of rewards was unpredictable. Taken together, the increased response in the anterior insula in anticipating an uncertain reward may bias adolescents towards increased risk-taking behavior.

One explanation that has to be considered is that the increased activation in the anterior insula reflects negative affect. Not winning might be associated with more experienced negative arousal when it occurs at the end of the trial (XXY) compared to when it occurs at the presentation of the second picture (XYZ). Even though we estimated the HRF at the onset of the second stimulus, the third stimulus followed 1.5 sec later. Therefore, it is possible that the observed neural response is influenced by the third stimulus. In future studies it will be important to further examine the effect of both the degree of risk/uncertainty and the amount of reward on adolescent decision-making. Given the possible focus of the adolescent group on reward, it would be interesting to test if the neural systems that are responsive to uncertainty respond similarly when the valence of the outcome is negative, i.e. when the XXX condition would reflect a loss rather than gain.

3.4.2 Developmental changes in outcome processing

As expected, winning money resulted in increased activation in the ventral striatum. This finding replicates previous studies that have

shown that this region is responsive to rewards (Huettel 2006; Knutson et al. 2001; McClure et al. 2003). Interestingly, striatal activation following a win peaked in 14-15-year-olds, and was less pronounced in 10-12-year olds, and 18-23-year-olds, consistent with the hypothesis that this region is more responsive in adolescents (Casey et al. 2008a; Ernst et al. 2006a; Galvan et al. 2006).

In the present study, we found the peak in responsiveness of the ventral striatum in middle adolescence only for reward processing, not for reward anticipation. This finding is inconsistent with previous studies, which reported an increase in activation in this region before the actual delivery of rewards. These prior results were taken to suggest a role for the ventral striatum in the prediction and anticipation of outcomes (Bjork et al. 2004; Galvan et al. 2006; Huettel 2006; Knutson et al. 2001). Our findings, however, suggest that the peak in ventral striatum response in adolescents is only found for the receipt of rewards. In previous experiments, the cues signaled potential rewards and allowed for reward prediction, therefore activation in the ventral striatum in these studies could reflect an early response to *knowing* that the reward will follow, rather than anticipating the *possibility* of a reward. These data could also be taken to suggest that adolescents overestimate their chances of obtaining a reward, or ability to obtain a reward. We suggest that in the present study a peak in activation in the ventral striatum was not observed until the actual delivery of reward because the task design maximized uncertainty and did not allow for reward prediction. Even though the anticipation results did not show a statistically significant peak in activation and no Age x Condition interaction in the ventral striatum, follow up analyses hinted that the anticipation striatum response was larger for young and middle adolescents relative to adults. Future studies should study the anticipation versus outcome results in more detail.

Finally, young adults, but not early and middle adolescents, showed increased activation in left lateral OFC following the omission of rewards. Lateral OFC has previously been implicated in processing of punishment (O'Doherty et al. 2001). The OFC is highly connected to both appetitive circuitry and other regions within the PFC, and recently it has been suggested that OFC has an integrative function by guiding the brains' response to affective information, and guiding affective decision making by maintaining and updating a representation of incentive related expectations online (for reviews, see (O'Doherty 2007;

Wallis 2007). The response of lateral OFC in young adults may therefore signal the need for increased attention and adjustment of behavior following negative outcomes. It should be noted that the OFC is a heterogeneous region and many questions regarding its role in goal directed behavior and decision making and associated changes with development need to be tested in future studies. The finding that this region is involved in the processing of unfavorable outcomes in adults, but not in early and middle adolescents, is consistent with the hypothesis that networks in the brain related to higher order processing and cognitive control functions do not mature until late adolescence (Ernst et al. 2006a; Galvan et al. 2006).

3.4.3 Conclusions

The current findings could be interpreted in light of recent accounts that seek a neuropsychological explanation for adolescent behavior. Both the Social Information Processing Network model (SIPN) (Nelson et al. 2005) and the Triadic Model (Ernst et al. 2006) contain an appetitive component and a cognitive/regulatory component. In these models, adolescent behavior is characterized by a strong appetitive system and a relatively weak control system. The SIPN Model (Nelson et al. 2005) suggests that the brain structures that underlie the appetitive component are responsive to gonadal hormones, and are triggered at the beginning of puberty, in contrast to cognitive structures that follow a slower development.

The passive paradigm used in the present study did not allow us to resolve questions about the way in which differences in the neural substrate of reward processing and risk perception between adolescents and adults contribute to motivated behavior in adolescents and adults. It is important to elucidate this relation and its developmental trajectory, because adolescent risky behavior can have serious consequences (Fareri et al. 2008; Steinberg 2004). The finding that reward related brain regions are more responsive in adolescence, even when rewards are unrelated to behavior and small, suggests fundamental differences in the way in which uncertain rewards are processed at different ages. In order to judge the ecological validity of these findings, future studies should take individual differences in for example sensation-seeking, temperament and gender into account and will have to examine these regions using more complex tasks. A second limitation of this study is that we did not obtain direct measures of pubertal status, which limits

our ability to interpret the contribution of pubertal changes to the differences between the 10-12 and 14-15-year-olds. Future studies should attempt to more closely relate age related changes to changes associated with pubertal development.

In summary, our findings demonstrate that brain activation patterns related to outcome anticipation in the absence of behavior are distinguishable from those related to the processing of outcomes. Anticipation of uncertain reward is associated with activation in the anterior insula and striatum. In particular, activation in the anterior Insula shows a linear developmental trend, and decreases from early adolescence to young adulthood. In contrast, processing of reward is associated with a peak in activation in the ventral striatum in 14-15-year-olds, and 10-12-year-olds to a lesser extent. Interestingly, 18-23-year-olds are most responsive to omitted reward, showing activation in lateral OFC regions. These findings support the hypothesis that adolescence is characterized by an imbalance in the maturation of affective and regulatory brain circuitry (Ernst et al. 2005; Galvan et al. 2006; May et al. 2004). The present data show that at a basic level of processing adolescents are more responsive to anticipated and received reward and risk associated with uncertainty compared to adults.

Supplemental Table 3.1 *MNI coordinates of peak activation voxels for significant clusters related to the anticipation of reward (XXY > XYZ contrast) for 10-12, 14-15 and 18-23-year-olds, significant at p < .001 uncorrected.*

Contrast	Region	MNI coordinates			Z-value	Cluster size (voxels)
XXY > XYZ						
10-12-year-olds						
	R anterior insula	36	24	-9	4.67	167
	L anterior insula	-33	18	9	4.23	10
	L anterior insula	-33	15	-15	4.19	90
	L caudate	-6	6	0	3.85	11
	R caudate	12	15	0	3.67	9
	L frontal lobe - Suppl. motor cortex	-3	6	57	3.48	32
	R parietal lobe - Sup. parietal	30	-45	42	3.84	47
	R parietal lobe - Supramarginal gyrus	51	-33	45	3.86	38
	L parietal lobe - Lateral occipital cortex	-27	-60	30	3.30	6
14-15-year-olds						
	R anterior insula	30	27	0	5.18	238
	L anterior insula	-33	15	6	3.74	71
	L ventral striatum - Accumbens	-9	9	-3	4.16	34
	R thalamus	9	0	0	4.52	98
	L thalamus	-6	-9	-3	4.00	27
	R frontal lobe – Paracingulate gyrus	9	15	48	3.44	7
	R frontal lobe – Precentral gyrus	54	9	27	4.01	41
	L frontal lobe – Precentral gyrus	-54	0	45	3.78	13
	R frontal lobe – Suppl. motor cortex	3	3	63	3.93	59
	R parietal lobe – Lateral occipital cortex	24	-66	36	4.33	137
	R occipital lobe – Lat. occipital cortex	30	-78	18	3.84	21
18-23-year-olds						
	R Anterior insula	33	27	0	5.16	35
	L Anterior insula	-33	21	6	3.91	11
	R parietal lobe – Lateral occipital cortex	33	-69	54	3.55	7

Supplemental Table 3.2 *MNI coordinates of peak activation voxels for significant clusters related to the processing of reward (XXX > XXY contrast), and to the processing of omitted rewards (XXY > XXX contrast) for 10-12, 14-15 and 18-23-year-olds, thresholded at p < .001 uncorrected.*

Contrast	Region	MNI coordinates			Z-value	Cluster size (voxels)
XXX > XXY						
10-12-year-olds						
	L frontal lobe – Inferior frontal gyrus	-36	12	27	3.91	10
	L caudate	-12	9	0	3.79	33
	L frontal lobe – Precentral gyrus	-54	-12	42	3.77	79
	R frontal lobe – Precentral gyrus	60	0	24	3.67	62
	L frontal lobe – Precentral gyrus	-54	3	24	3.52	22
	L frontal lobe - Paracingulate gyrus	-3	18	45	3.50	28
	L frontal lobe – Superior frontal gyrus	-18	12	48	3.37	5
	L parietal lobe – Supramarginal gyrus	-63	-45	24	3.35	6
	L putamen	-18	18	-12	3.28	6
	L frontal lobe – Middle frontal gyrus	-42	36	24	3.26	5
14-15-year-olds						
	L caudate	-15	3	21	4.40	283
	L parietal lobe – Supramarginal gyrus	-51	-39	45	4.30	179
	R anterior insula	30	15	-15	4.29	18
	L parietal lobe - Parahippocampal gyrus	-12	-33	-9	4.28	497
	L frontal lobe - Paracingulate gyrus	-6	18	42	4.21	122
	R temporal lobe – Fusiform cortex	39	-21	-15	4.04	5
	L parietal lobe - Posterior cingulate gyrus	-3	-39	27	4.01	130
	L anterior insula	-39	3	-3	3.98	110
	L frontal lobe – Frontal pole	-24	60	-3	3.95	9
	L frontal lobe – Subcallosal cortex	-12	21	-18	3.92	7
	R occipital lobe – fusiform gyrus	15	-87	-15	3.86	41
	L Thalamus	-15	-36	9	3.83	8
	L frontal lobe – Middle frontal gyrus	-42	33	27	3.82	32

	R temporal lobe – Inf. temporal gyrus	57	-30	-18	3.73	24
	L frontal lobe – Paracingulate gyrus	-15	36	24	3.67	24
	R temporal lobe – Inf. temporal gyrus	57	-54	-18	3.63	5
	L occipital lobe – Precuneus cortex	-3	-78	36	3.62	32
	R parietal lobe – Postcentral gyrus	21	-42	54	3.55	6
	L frontal lobe – Precentral gyrus	-51	-9	39	3.53	20
	L parietal lobe – Supramarginal gyrus	-57	-48	15	3.49	6
	R frontal lobe – Anterior cingulate gyrus	3	30	15	3.48	40
	M frontal lobe – Frontal pole	0	57	3	3.45	17
	Cerebellum	0	-63	-15	3.43	7
	M parietal lobe – Post. cingulate gyrus	0	-24	24	3.32	5
18-23-year-olds						
	R occipital lobe – Intracalcarine cortex	15	-81	6	3.67	6
	L occipital lobe – Occipital pole	-15	-102	-3	3.55	32
	L occipital lobe – Occipital pole	-30	-93	-12	3.44	13
XXY > XXX						
10-12-year-olds						
	R temporal lobe – Fusiform cortex	-24	-48	-15	3.64	12
	R parietal lobe – Precuneus cortex	24	-54	6	3.31	5
	L temporal lobe – Fusiform gyrus	-39	-66	-18	3.26	7
14-15-year-olds						
	No significant clusters					
18-23-year-olds						
	L frontal lobe – Frontal orbital cortex	-27	36	-12	4.20	7
	L frontal lobe – Frontal pole	-9	54	-18	3.79	9