Title

A cross-sectional and longitudinal analysis of reward-related brain activation: Effects of age, pubertal stage, and reward sensitivity

Authors

van Duijvenvoorde, Anna CK
de Macks, Zdeňa A Op
Overgaauw, Sandy
et al.

Publication Date

2014-08-01

DOI

10.1016/j.bandc.2013.10.005

Peer reviewed

Brain and Cognition 89 (2014) 3–14

Contents lists available at ScienceDirect

Brain and Cognition

journal homepage: www.elsevier.com/locate/b&c

A cross-sectional and longitudinal analysis of reward-related brain activation: Effects of age, pubertal stage, and reward sensitivity ☆

Anna C.K. van Duijvenvoorde [a,b,*,1], Zdeňa A. Op de Macks [c,1], Sandy Overgaauw [a,b], Bregtje Gunther Moor [a,b], Ronald E. Dahl [c], Eveline A. Crone [a,b]

[a] Faculty of Social Sciences, Leiden University, The Netherlands
[b] Leiden Institute for Brain and Cognition (LIBC), Leiden, The Netherlands
[c] University of California, Berkeley, USA

ARTICLE INFO

Article history:
Available online 7 February 2014

Keywords:
Risk taking
Ventral striatum
Medial prefrontal cortex
Adolescence
Functional connectivity
BAS-score

ABSTRACT

Neurobiological models suggest that adolescents are driven by an overactive ventral striatum (VS) response to rewards that may lead to an adolescent increase in risk-taking behavior. However, empirical studies showed mixed findings of adolescents' brain response to rewards. In this study, we aimed to elucidate the relationship between reward-related brain activation and risky decision-making. In addition, we examined effects of age, puberty, and individuals' reward sensitivity. We collected two datasets: Experiment 1 reports cross-sectional brain data from 75 participants (ages 10–25) who played a risky decision task. Experiment 2 presents a longitudinal extension in which a subset of these adolescents ($n = 33$) was measured again 2 years later. Results showed that (1) a reward-related network including VS and medial PFC was consistently activated over time, (2) the propensity to choose the risky option was related to increased reward-related activation in VS and medial PFC, and (3) longitudinal comparisons indicated that self-reported reward sensitivity was specifically related to VS activation over time. Together, these results advance our insights in the brain circuitry underlying reward processing across adolescence.

1. Introduction

Adolescence is characterized as a period of hormonal changes and pronounced changes in social-affective engagement such as increases in sensation seeking and risk taking. Neurobiological models of adolescent development have suggested that adolescents are more sensitive to rewards due to a relatively increased limbic response in combination with reduced down-regulation by the prefrontal cortex and other cortical areas (Ernst & Fudge, 2009; Nelson, Leibenluft, McClure, & Pine, 2005; Somerville, Jones, & Casey, 2010). Accordingly, these models suggest that such neurobiological changes may underlie typical adolescents' risky behaviors such as substance abuse, unsafe sexual behavior, and reckless driving (Dahl, 2004; Steinberg et al., 2008).

A typically found 'reward-network' in the brain includes dopamine-rich areas in the midbrain and their targets: striatum and medial prefrontal cortex (Blakemore & Robbins, 2012; Clark, Lawrence, Astley-Jones, & Gray, 2009; Tom, Fox, Trepel, & Poldrack, 2007). More specifically, ventral striatum (VS) has been implicated in anticipating and processing different types of rewards, as well as in producing learning signals known as prediction errors (Cohen et al., 2010; Delgado, 2007; Galvan et al., 2005; Knutson, Fong, Adams, Varner, & Hommer, 2001). Similarly, medial PFC – specifically the part that overlaps with the anterior cingulate cortex (ACC) – is also related to prediction-error coding (Van den Bos, Cohen, Kahnt, & Crone, 2012), but also to action-related reward associations (Kennerley & Walton, 2011; Rushworth, Noonan, Boorman, Walton, & Behrens, 2011), and detecting the need for increased control (Ridderinkhof, Ullsperger, Crone, & Nieuwenhuis, 2004). In contrast, a more ventral region of the medial prefrontal cortex, adjacent to medial orbital frontal cortex, has been implicated in coding rewards and is linked to representations of 'value' (Kuhnen & Knutson, 2005; McKell Carter, Meyer, & Huettel, 2010). Moreover, research indicates strong interconnections between the VS and several parts of the medial PFC. These so-called striatal-cortical

☆ This research was supported by a VIDI grant and an ERC grant awarded to Eveline A. Crone.

* Corresponding author. Address: Faculty of Social Sciences, Leiden University, Wassenaarseweg 52, 2333AK Leiden, The Netherlands.
E-mail address: a.c.k.vanduijvenvoorde@fsw.leidenuniv.nl (A.C.K. van Duijvenvoorde).

[1] Both authors contributed equally.

http://dx.doi.org/10.1016/j.bandc.2013.10.005
0278-2626/

loops may be important for regulating reward-related responses and subsequent goal-directed behavior (Haber & Knutson, 2010). Together, these findings suggest that goal-directed behavior (e.g., risk taking) is driven by a reward-valuation system, in which VS encodes the more 'basic' aspects of reward and medial PFC integrates the different aspects of the reward to represent its subjective value and is important for selecting actions and controlling behavior.

Results of previous developmental functional MRI studies suggest that adolescent decision-making may be biased by a relatively hypersensitive VS response to rewards. That is, research has indicated that adolescents (ages 13–17 years) show a larger VS response to rewards compared to children and adults (Galvan et al., 2006; Padmanabhan, Geier, Ordaz, Teslovich, & Luna, 2011; Van Leijenhorst, Gunther Moor, et al., 2010; Van Leijenhorst, Zanolie, et al., 2010). However, other studies have indicated striatal hypo-activation in adolescents during reward anticipation (Bjork et al., 2004; Bjork, Smith, Chen, & Hommer, 2010) or have shown little differences between adolescents and adults in VS response to rewards (May et al., 2004; Paulsen, McKell Carter, Platt, Huettel, & Brannon, 2012). Moreover, only some studies have found that the VS response to rewards correlates with risk-taking behavior in every-day life (Galvan, Hare, Voss, Glover, & Casey, 2007). Thus, several questions remain with respect to the specificity of the VS and medial PFC responses to rewards in adolescence and their relationship to risky behavior. For instance, it remains to be determined whether higher risk-taking in adolescence is associated with a higher VS response to rewards, a lower medial PFC response, or less functional connectivity between these areas (see also Cohen et al., 2012; Van den Bos et al., 2012).

Mixed findings in adolescents' reward-related brain activation might have several causes, such as differences in task design and analyses (Galvan, 2010). In addition, prior contradictory findings may point toward individual differences in adolescence (Somerville et al., 2010). One important source of influences on subcortical and cortical responses could be pubertal development, which may serve as an important individual difference measure in adolescents' brain activation in response to rewards and appetitive cues. That is, gonadal hormone levels significantly increase during adolescence and have both organizational and activating effects on brain functioning (Blakemore, Burnett, & Dahl, 2010; Sisk & Zehr, 2005). For instance, higher testosterone levels have been associated with increased VS activation (Forbes et al., 2010; Op de Macks et al., 2011) and to adolescent typical risk-behavior such as experimentation with alcohol (De Water, Braams, Crone, & Peper, 2013).

Another possible source to explain individual differences in reward-related brain activation could be a persons' sensitivity to rewards. For instance, prior studies reported that activation in the VS correlated positively with self-reported (1) reward sensitivity, as measured by the behavioral approach system (BAS) scale (Beaver et al., 2006), (2) sensation seeking, as measured by the brief sensation-seeking scale (Bjork, Knutson, & Hommer, 2008), (3) impulsivity, as measured by the psychopathic personality inventory (Buckholtz et al., 2010), and (4) real-life risk taking (Galvan et al., 2007). Possibly, these personality differences in reward-related response tendencies may explain why some adolescents are more responsive to rewards than others.

In the current study we examined reward processing in adolescence in more detail. Specifically, we aimed to elucidate the relationship between reward-related brain activation, frontostriatal connectivity strength, and behavior. In addition, we focused on examining effects of age, pubertal development, and individual's self-reported reward sensitivity on reward-related brain activation. To these ends, we report two experiments using a risky decision task, in which participants could choose to take a gamble (and win or lose 10 Eurocents) or pass on this gamble (in which case nothing was gained or lost). We were specifically interested in the brain's response to rewards and losses as a result of an active gamble, since prior studies have shown that outcome monitoring is more salient when the outcomes are the result of an active choice (Rao, Korczykowski, Pluta, Hoang, & Detre, 2008; Tricomi, Delgado, & Fiez, 2004).

In the first experiment, we reanalyzed the adolescent sample (ages 10–16 years) previously reported by Op de Macks et al. (2011) and added a young–adult sample (18–25 years). The study by Op de Macks et al. (2011) primarily examined individual differences in the reward-related brain activation in relation to testosterone levels, but made no age comparisons. In the current study, we studied age, puberty, and individual differences in reward sensitivity in the same sample. The second experiment included a longitudinal extension of Experiment 1. That is, a subset of the adolescents from Experiment 1 was re-invited 2 years later, and completed the same risky decision task. This combined cross-sectional/longitudinal approach presents unique insights in the development of the reward system across adolescence and allows us to link changes in reward-related activation to individual's changes in behavior, age, pubertal development, and reward sensitivity.

Replicating prior studies, we expected to observe activation in VS and medial PFC when processing rewards. Second, we predicted that risk-taking propensity would be positively correlated with VS activation, negatively correlated with medial PFC activation and/or the strength of connectivity in this reward network. Third, based on prior findings we expected VS activation to change with age (quadratic or linear). Finally, we tested whether the VS response to rewards was related to pubertal development, or to self-reported reward-sensitivity (as measured with the self-report BAS scale).

2. Methods Experiment 1

2.1. Participants

Seventy-eight right-handed participants (50 adolescents, 28 adults) were scanned while performing a risky decision task. All participants reported an absence of neurological or psychiatric impairments (on a brief screening module) and provided written informed consent for the study (parental consent and participant assent for minors). The cross-sectional adolescent data has been reported before in Op de Macks et al. (2011), but that study focused primarily on the association between individual differences in reward-related brain activation and testosterone levels in adolescents and did not examine age effects across adolescence. The goal of this study was to extend this (cross-sectional) data set by including a sample of young adults. All procedures were approved by the local Medical Ethics Committee.

Three participants (ages 12, 15, and 16) showed head motion exceeding 3 mm during scanning and were therefore removed from further analyses. Accordingly, the final sample consisted of 75 participants (10–25 years, *Mean* = 15.9 years, *SD* = 4.1, 47 females). Mean head motion correlated with Age, $r = -.27$, $p = .02$, but was overall low, *Mean* = 0.85 mm, *SD* = .04. Pubertal development was measured for all adolescents (10–16-year-olds, $n = 47$, 32 females), using the Pubertal Development Scale (PDS; Petersen, Crockett, Richards, & Boxer, 1988).[2] No PDS scores were obtained for the young adults, since we presume all of the adult subjects have completed puberty. PDS score was positively correlated with age in the adolescent group, $r = .62$, $p < .001$.

[2] The reason for choosing PDS as a puberty index instead of testosterone levels was because PDS measures were available for adolescents in both experiments (cross-sectional and longitudinal).

Participants completed two subscales (similarities and block design) of the Wechsler Intelligence Scale for Children or the Wechsler Intelligence Scale for Adults in order to obtain an estimate of their intelligence quotient (Wechsler, 1991; Wechsler, 1997). Estimated IQ scores correlated negatively with Age, $r = -.4$, $p < .01$. Therefore IQ was included as a covariate of no-interest in further analyses.

2.2. Task

Participants performed the Jackpot Task, a risky decision task that has been used to assess developmental changes in reward processing and risk-taking behavior (Op de Macks et al., 2011; see Fig. 1). In the Jackpot task, participants were presented with a slot machine with two of the three slots showing the same fruit. Participants were requested on each trial to choose between the risky option 'spin' (i.e., *play*), or the safe option 'reset' (i.e., *pass* trial). A *play* decision was indexed by a button press with the right index finger; a *pass* decision was indicated by a button press with the left index finger. The choice to play led to a monetary reward or loss (10/−10 Eurocents), whereas the choice to pass a trial led to no monetary reward or loss (0 Eurocents). The chance to win was indicated by pictures of the possible fruits for the third slot, which were visible to the participants. The chance to win varied between trials (66% versus 33%), although eventually rewards and losses occurred in 50% of the cases for both trials. Participants played 50 trials in total (30 high risk trials and 20 low risk trials) and for current analysis purposes all trials were averaged. In the prior study by Op de Macks et al. (2011) it was found that the reward-related brain activation did not differ between high and low-risk rewards. Therefore, averaging across these trials increased the power of the dependent measure. On average, there were 17 loss trials and 17 reward trials. Participants were given initial play money (2 Euros), and were instructed that they would be paid (in real money) according to the final outcome at the end of the experiment.

We focused specifically on the outcome phase after play choices, since the design was not optimal to study the feedback and the decision phase separately. That is, 'pass' trials were followed by 'reset feedback' and 'play' trials were followed by valence feedback. Given the short time window between choice and feedback, the choice trials were confounded by feedback type. For this reason, our analysis focused on the play trials, which were unpredictably followed by reward or loss.

Each trial started with a centrally presented fixation cross, followed by the stimulus presentation (3000 ms). During this time participants had to select a choice (play or reset) by a button press. Subsequently, feedback was given (reward, loss or reset) for 2000 ms. If no timely response was given, the text 'too slow!' was presented for 2000 ms, followed by the next trial. This happened rarely, in less than .02% of the trials. Between trials a fixation cross was presented for 1–6 s, jittered in steps of 500 and 1000 ms.

2.3. Procedure

Before entering the scanner, participants received instructions and briefly practiced the task. All scanning procedures were explained using a mock scanner. The Jackpot task was acquired in a single run that lasted approximately 5 min. The task was one of a battery of four tasks and was presented first in the battery (for results of the other tasks, see Gunther Moor et al., 2012) lasting a total of approximately 50 min. Self-report measures were administered immediately after the scan in a separate room; for the adults, the BIS/BAS questionnaire was administered at home.

2.4. Reward sensitivity

Reward sensitivity was measured using the behavioral inhibition system/behavioral approach system scale (BIS/BAS; Carver & White, 1994). A recent study examined the psychometric characteristics of the Dutch version of Carver and White's (1994) BIS/BAS scales in two large independent samples of early and mid-adolescents; their findings confirmed that "the scales are suitable for use in research settings" (p. 500; Yu, Branje, Keijsers, & Meeus, 2011). The BIS/BAS scales consist of 24 items across four scales: one BIS scale that measures punishment sensitivity and three BAS scales that measure reward sensitivity. Note that in the current study we were specifically interested in the BAS scales. The BAS Drive scale measures the persistent pursuit of desired goals, the BAS Fun Seeking scale measures both desire for new rewards and willingness to approach potentially rewarding events on the spur of the moment, and the BAS Reward Responsiveness scale measures the positive response to (the anticipation of) reward. Higher scores indicate greater reward sensitivity. Seventeen young adults (7 females) did not fill out the BIS/BAS scale, leaving a total of $n = 58$ who filled out the BIS/BAS scale.

2.5. MRI data acquisition

fMRI data were acquired with a standard whole-head coil using a 3-T Philips Achieva scanner. $T2^*$-weighted echoplanar images (EPI's) were obtained during one functional run, in which the first two volumes were discarded to allow for equilibration of T1 saturation effects. Volumes covered the whole brain (38 slices; 2.75 mm slice thickness; interleaved acquisition) and were acquired every 2200 ms (TE = 30 ms). A high resolution T1 image

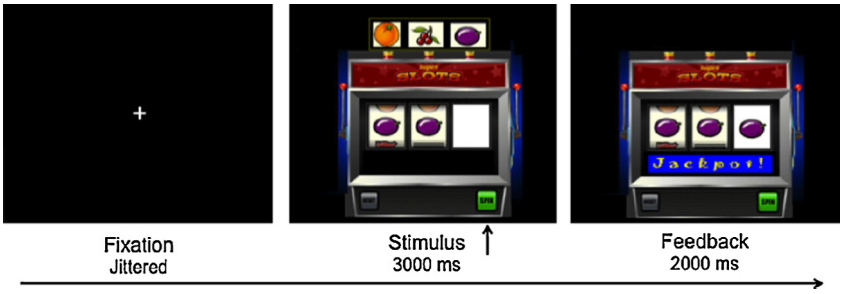

Fig. 1. The Jackpot task (Op de Macks et al., 2011). Example of a trial in which the participant is presented with a 1/3 chance of a reward (+10) and a 2/3 chance of a loss (−10). The participant decides to play by pressing the right button and which results in a reward (feedback screen). Reprinted from "Testosterone levels correspond with increased ventral striatum activation in response to monetary rewards in adolescents" by Z.A. Op de Macks, B. Gunther Moor, S. Overgaauw, B. Güroğlu, R.E. Dahl, & E.A. Crone, *Developmental Cognitive Neuroscience, 1*, 506. Reprinted with permission.

was collected at the end of each scan session, together with a high-resolution T2-weighted anatomical scan with the same slice prescription as the EPIs. Visual stimuli were projected onto a screen that was visible for participants via a mirror attached to the head coil. Head motion was restricted due to foam inserts that surrounded the head.

2.6. fMRI preprocessing and statistical analysis

Data preprocessing and analysis were conducted using SPM8 (Wellcome Department of Cognitive Neurology, London). Images were corrected for differences in timing of slice acquisition, followed by rigid body motion correction. The T1 structural image was coregistered to the functional images and segmented according to gray matter, white matter, and cerebrospinal fluid. Functional images were then spatially normalized using the normalization parameters obtained from the segmentation procedure. For seven adolescents no T1 was obtained, due to time constraints or technical problems, in which case functional volumes were spatially normalized to EPI templates. The normalization algorithm used a 12-parameter affine transformation together with a nonlinear transformation involving cosine basis functions. During normalization the data was re-sampled to 3-mm cubic voxels. Templates were based on the MNI305 stereotaxic space (Cocosco, Kollokian, Kwan, & Evans, 1997). Functional volumes were smoothed with a 6-mm full-width at half maximum isotropic Gaussian kernel.

Statistical analyses were performed on individual subjects' data using the General Linear Model (GLM) in SPM8. The fMRI time series data were modeled by a series of events convolved with a canonical hemodynamic response function. In a whole-brain analysis, reward and loss outcomes were modeled as single events with zero duration at the onset of the presentation of the outcome. This whole-brain analysis focused on the contrast [reward > loss]. Reset trials and trials on which the participant did not respond within the 3-s time frame were modeled separately, but were not included in contrasts.

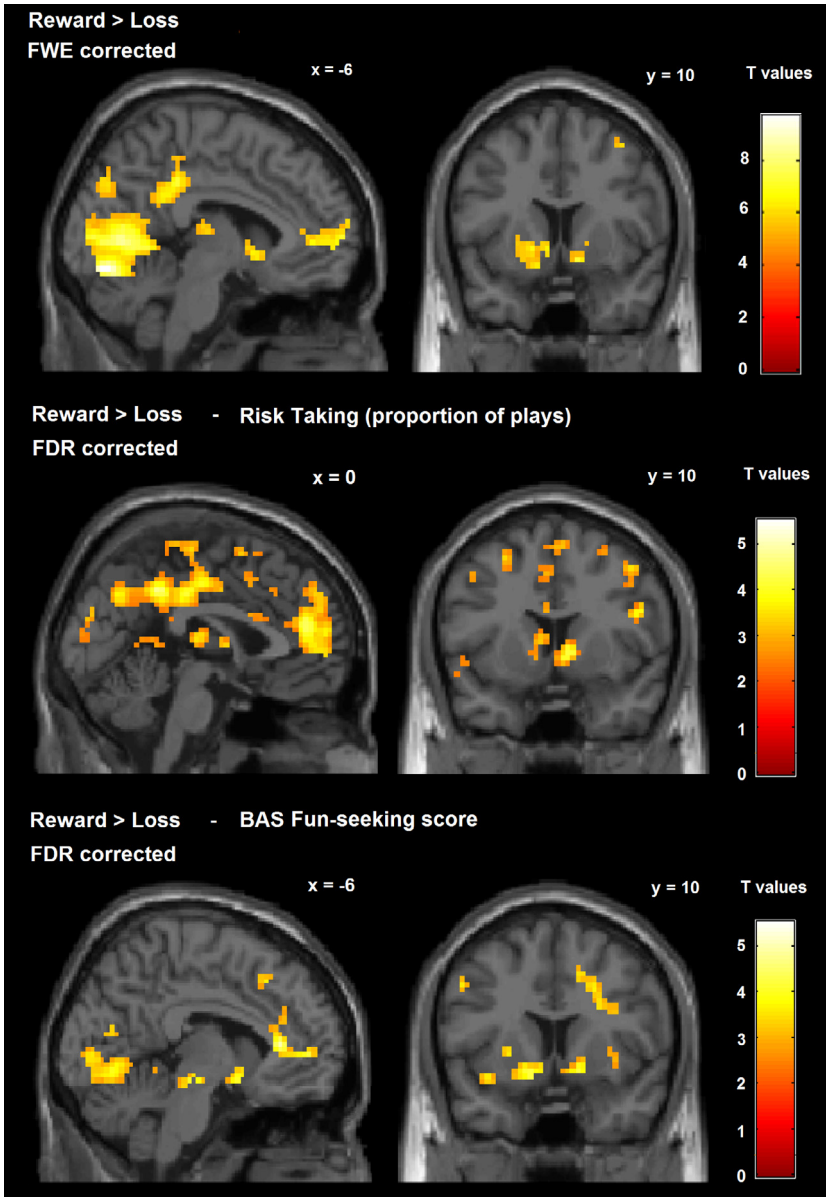

Fig. 2. Whole-brain results for the contrast [reward > loss] for all participants, at an FWE corrected threshold of $p < .05$, >10 contiguous voxels (upper panel). Whole brain results for the contrast [reward > loss], displaying regions that showed increased activation with increased number of plays (middle panel) and displaying regions that showed increased activation with increasing BAS Fun-seeking score (lower panel). Both results are reported at an FDR corrected threshold of $p < .05$, >10 contiguous voxels.

Table 1
Coordinates for the brain regions showing activation for the reward > loss contrast and brain regions showing a positive correlation in the reward > loss contrast with proportion of plays and self-reported BAS Fun-seeking, peak voxels are reported at cluster level. PFC = prefrontal cortex, VS = ventral striatum, ACC = anterior cingulate cortex, BA = brodmann area.

Anatomical area	Cluster size	MNI coordinates (mm)			Z-max value
		x	*y*	*z*	
Reward > loss, FWE corrected p < .05, >10 contiguous voxels					
L VS	100	−15	15	−6	6.87
R VS	32	12	9	−9	6.23
R ACC (BA24)	38	6	0	33	5.46
L posterior cingulate cortex	213	−6	−36	36	6.23
L lateral PFC	88	−42	45	12	6.36
L superior frontal gyrus	106	−21	33	45	6.76
L superior frontal gyrus	99	−12	66	15	6.22
R middle frontal gyrus	16	39	9	54	5.34
R precentral gyrus	58	21	−27	60	5.93
R precentral gyrus	12	42	−15	60	5.57
L precentral gyrus	23	−21	−30	60	5.71
R putamen	11	30	−12	−12	6.10
L thalamus	25	−6	−18	9	5.25
L angular gyrus	75	−39	−69	39	5.55
R inferior parietal lobe	32	42	−42	57	5.31
R superior parietal lobe	15	18	−54	66	5.00
L middle temporal gyrus	10	−57	−45	6	5.09
L occipital lobe/lingual gyrus	1830	−12	−78	−15	7.82
Proportion of plays, FDR corrected, p < .05, >10 contiguous voxels					
R ACC/(para)cingulate gyrus	887	3	45	18	4.43
R (para)cingulate gyrus	72	9	18	45	3.47
L ACC (BA24)	20	−3	12	24	2.98
R lateral PFC	131	45	15	48	3.84
L middle frontal gyrus	24	−27	9	54	3.38
R middle frontal gyrus	11	30	12	57	3.11
R superior frontal gyrus	20	18	42	39	3.35
L inferior frontal gyrus	59	−39	24	−9	3.61
R inferior frontal gyrus (BA9)	41	51	9	24	3.79
R inferior frontal gyrus (BA47)	12	45	21	−6	2.85
L precentral gyrus	67	−45	−3	45	4.38
L postcentral gyrus	56	−51	−21	48	3.38
R supplementary motor area	39	3	6	60	3.51
R thalamus (including striatum)	339	9	−21	12	4.36
R middle temporal gyrus	25	45	−54	6	3.15
L posterior cingulate cortex	23	−3	−45	6	3.13
L intracalcarine cortex	191	−24	−66	9	4.28
L precuneus/occipital lobe	3047	−15	−54	39	5.26
BAS Fun-seeking scale, FDR corrected, p < .05, >10 contiguous voxels					
L ACC	135	−9	33	9	4.65
R ACC (BA24)	17	9	21	27	3.05
L paracingulate gyrus	16	−6	24	45	3.37
L VS (putamen)	235	−18	12	−9	4.08
R VS (putamen)	18	27	−3	−3	3.23
L brainstem	103	−9	−21	−12	4.18
R superior frontal gyrus	58	15	33	48	3.97
R middle frontal gyrus	22	33	21	42	3.53
L middle frontal gyrus	87	−33	27	45	3.46
R inferior frontal gyrus	24	42	33	0	3.41
R cingulate gyrus	87	15	6	45	4.01
L precentral gyrus	14	−45	0	33	3.42
R insula	38	27	24	9	3.82
R insula	11	36	6	0	3.06
R parietal lobe (precuneus)	77	15	−48	39	3.63
R parietal lobe (angular gyrus)	15	36	−51	39	3.32
L parietal lobe (angular gyrus)	13	−33	−60	39	2.98
R superior parietal lobe	11	15	−51	69	3.22
L intracalcarine cortex	19	−3	−69	15	3.18
L occipital lobe/PCC	2261	−15	−45	−3	4.88
L occipital lobe (cuneus)	34	−21	−72	18	3.45
L lateral occipital cortex	14	−12	−84	36	3.26
L lateral occipital cortex	11	−45	−63	21	2.89

Task-related responses were considered significant if they consisted of at least 10 contiguous voxels that exceeded a family-wise error (FWE) or a false discovery (FDR) corrected threshold of $p < .05$ (see Results). For region of interest (ROI) analyses the MarsBaR toolbox in SPM8 was used (Brett, Anton, Valabregue, & Poline, 2002).

2.7. Psycho-physiological interaction

To study the interplay between VS and other brain regions during processing of rewards compared to losses, functional connectivity was assessed using psychophysiological interaction (PPI) analysis (Friston et al., 1997). In PPI, functional connectivity is de-

fined as significantly correlated hemodynamic response patterns over time between brain regions as a function of the experimental task context, here reward versus loss processing. Note that this method does not imply directionality of connectivity between regions.

The seed region in the PPI analysis was the right and left VS mask based on the reward > loss whole-brain contrast. Since VS was bilaterally activated, two separate PPIs were conducted with the right and left VS mask. By means of a peak-detection algorithm, we detected a peak voxel of activation per participant within the (left and right) VS mask. Around this peak voxel a sphere of 7 mm was drawn to create a seed ROI. After the extraction of the time course from the VS mask and the psychological vector of interest (weighting rewards with 1 and losses with −1), their interaction term was computed. This interaction regressor indicated which brain regions are functionally correlated with the respective seed VS mask. In other words, the resulting estimates from this interaction regressor express the extent to which activity in each voxel correlates with the seed region more when processing a reward than when processing a loss.

3. Results and discussion Experiment 1

3.1. Behavior

The average proportion of '*play*' decisions was .67 (range = .28–1, *SD* = .14). A linear regression with proportion of *plays* as a dependent and Age as an independent variable showed no significant effect of Age (*p*'s > .1). Similar analyses with PDS score, and the BAS scales (Drive, Fun-seeking, and Reward-responsiveness) as an independent variable, also showed no significant effects of PDS or BAS scores on proportion of plays (*p*'s > .1). Together these results reveal that the tendency to make a risky decision was not related to age, pubertal development or individual's reported reward sensitivity. Note that this resulted in an approximately equal number of trials in the neuroimaging analyses across ages.

3.2. Whole-brain analyses

Results for the contrast [reward > loss; FWE corrected, $p < .05$, >10 contiguous voxels] across all participants revealed bilateral VS activation and a cluster of activation in the medial PFC (see Fig. 2). Reward-related activation was also found in the posterior cingulate cortex (PCC), and other frontal and parietal brain regions (see Table 1 for regions of activation and their coordinates). No significant results were found for the opposite contrast [loss > reward].

The first question we aimed to address was the relation between reward-related brain activation and proportion to play (i.e., gamble) in the Jackpot task. To detect brain regions in which reward-related activation correlated with behavior, proportion of plays was added as a regressor of interest in a whole-brain analysis [reward > loss], and IQ was included as a covariate. At an FWE corrected threshold, $p < .05$, >10 contiguous voxels, no regions were detected. At an FDR corrected threshold of $p < .05$, >10 contiguous voxels, proportion of plays showed a positive association with reward-related activation in VS, medial PFC, PCC, thalamus, and other frontal brain regions (see Fig. 2 and Table 1 for regions of activation and their coordinates). No significant results were found for a negative association with proportion of plays. Thus, VS and medial PFC were more active following rewards, for those individuals who more often played.

The next question we aimed to address was the relation between reward-related brain activation and individual differences in BAS scores (BAS drive, BAS Fun-seeking, and BAS reward-responsiveness). BAS subscales were added as regressors of interest in a whole-brain analysis [reward > loss, $n = 58$], and IQ was included as a covariate. At an FWE corrected threshold ($p < .05$, >10 contiguous voxels), no regions were detected. At an FDR-corrected threshold of $p < .05$, 10 contiguous voxels, only the BAS Fun-seeking score showed a positive association with reward-related activation in VS, medial PFC, thalamus, and other frontal and parietal brain regions (see Fig. 2 and Table 1 for regions of activation and their coordinates). No significant results were found for a negative association with BAS scores. Thus, VS and medial PFC were more active following rewards, for individuals who in every-day life are more willing to approach a potentially rewarding event on the spur of the moment, as measured by items such as "I'm always willing to try something new if I think it will be fun", and "I crave excitement and new sensations" (Carver & White, 1994).

Finally, we addressed the relation between reward-related brain activation and age, based on prior studies that reported a peak in adolescence in response to rewards (Ernst et al., 2005; Galvan et al., 2007; Van Leijenhorst, Gunther Moor, et al., 2010; Van Leijenhorst, Zanolie, et al., 2010). To detect brain regions in which reward-related activation correlated with linear and quadratic changes in age, Age and Age^2 were included as regressors of interest in a whole-brain analyses, with IQ included as a covariate. No results survived FWE or FDR correction. Lowering the threshold to an uncorrected $p < .001$ level, indicated a cluster of linearly increasing activity in left putamen ($x = -24$, $y = 6$, $z = 9$, 33 voxels), but no regions were found when testing for a linear decrease or a quadratic pattern. A similar whole-brain analyses to test the relation between reward-related brain activation and puberty ($n = 47$) also showed no significant cluster of activation, not even at an uncorrected threshold of $p < .001$.

Thus, in the current study, we found no evidence for a peak in the brain's response to rewards in mid-adolescence, and weak evidence for a monotonic age-related increase in reward-related activation. Instead, these results indicate that reward-related brain activation was predominantly related to propensity to play and self-reported individual differences in fun seeking across adolescence.[3]

3.3. Functional connectivity

A final question was whether *connectivity* in a VS-medial PFC network was related to proportion of plays and other individual difference measures. For this purpose, two whole-brain PPI analyses with left VS and right VS masks from the whole-brain analysis (see Fig. 2, upper panel) as seed regions showed that processing rewards compared to losses enhanced functional connectivity between VS and medial PFC (including ACC and dorsal medial PFC regions; FDR corrected, $p < .05$, >10 contiguous voxels). Analyses for left VS and right VS pointed to partly overlapping regions, including medial PFC, visual cortex, and other frontal-parietal brain regions. However, functional connectivity with left VS showed an additional cluster in right anterior insula (see Fig. 3A and Supplementary Tables 1 and 2 for functionally connected regions and their coordinates).

We extracted the strength of functional connectivity between medial PFC and left VS, medial PFC and right VS, and right anterior insula and left VS for each participant. We tested whether the

[3] When including BAS-subscales (Drive, Fun seeking, and Reward responsiveness), proportion of plays, Age, and IQ as a covariate of no interest, in one whole-brain analyses the reported effects on the BAS Fun-seeking scale and Age generally remained. Only proportion of plays showed a weakened effect, in which an association with reward-related activity was observed specifically in medial PFC and only at an uncorrected threshold of $p < .001$,>10 contiguous voxels.

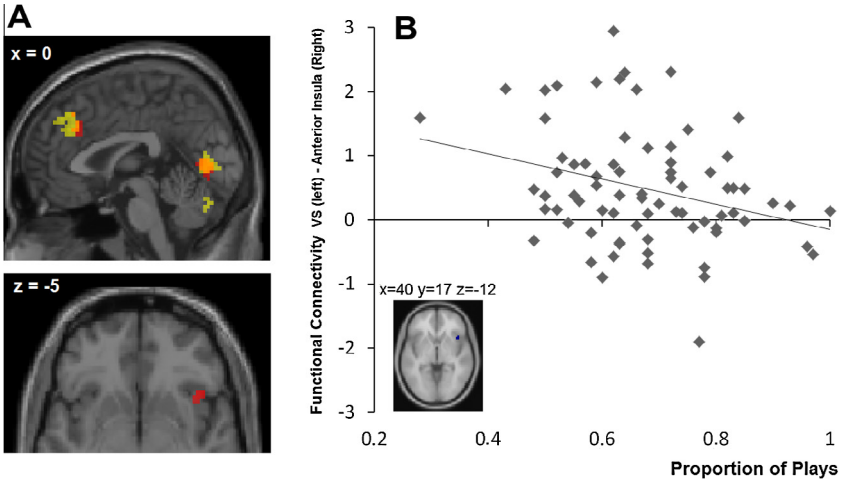

Fig. 3. (A) Whole-brain results for the psycho-physiological interaction regressor with a seed region in left VS (red) and right VS (yellow)––orange indicates overlap––at an FDR-corrected threshold of $p < .05$, >10 contiguous voxels. The interaction regressor shows regions that enhance functional connectivity with VS (left and right respectively) when processing rewards compared to losses. (B) Scatterplot depicting the positive association between functional connectivity between left VS–right anterior insula and proportion of plays. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

strength of these functional connections was correlated with individual's proportion of plays, age, pubertal development, and BAS-scores. Results indicated no significant results for functional connectivity strength between medial PFC and (left and right) VS. However, functional connectivity between right anterior insula and left VS was related to proportion of plays in the task, in which larger connectivity was related to a lower number of plays, $r = -.30$, $p < .02$ (see Fig. 3B).

3.3.1. Summary Experiment 1

Taken together, whole-brain analyses revealed that rewards compared to losses activated a reward-related brain network, including VS and medial PFC. Whole-brain results indicated that reward-related activation in these regions was positively associated with proportion of plays and self-reported reward sensitivity (as measured by BAS Fun Seeking-score). PPI analyses indicated increased functional connectivity after reward compared to losses between bilateral VS and (dorsal) medial PFC. Functional connectivity between left VS and right anterior insula also increased after rewards compared to losses, and this connectivity was associated with attenuated risky decision-making.

These cross-sectional results led to specific points of focus for the longitudinal analyses in Experiment 2. That is, in Experiment 2 we examined whether reward-related activation of VS and medial PFC [as defined by reward > loss activation] was related to changes in behavior, age and/or pubertal stage, and self-reported reward sensitivity over time.

4. Methods Experiment 2

4.1. Participants

A subset of the adolescents from Experiment 1 ($n = 33$) were scanned again approximately 2 years later, and were administered the same risky decision task. The goal of this study was to extend this dataset with a longitudinal sample. All participants signed informed consent (parental consent and participant assent for minors) and procedures were approved by the local Medical Ethical Committee.

Two participants showed head motion exceeding 3 mm during scanning at time point 2 (T2) and were therefore removed from further analyses. For longitudinal analyses, 31 adolescents were included at time point 1 (T1) and T2 (T1: 10–16-years-old, *Mean* = 13.1 years, *SD* = 2.0; T2: 12–19-years-old, *Mean* = 15.3 years, *SD* = 2.1, 18 female). The average time difference between the first and second scan was 2.13 years (1.8–2.3 years, *SD* = .14). The average head motion on T1 was significantly correlated with Age at T1, $r = -.41$, $p < .05$, however, head motion at T2 was not related to Age at T2, $p = .2$. Note that the mean head motion was low at both time points (T1: *Mean* = .1 mm, *SD* = .05; T2: *Mean* = .09 mm, *SD* = .04).

Similarly to T1, PDS scores at T2 were positively correlated with age at T2 ($r = .39$, $p < .05$). A repeated measures ANOVA indicated an increase in pubertal development from T1 to T2, $F(1,30) = 32.8$, $p < .001$, that did not differ significantly between boys (*Mean* PDS increase = .83) and girls (*Mean* PDS increase = .76), $p = .8$.

The task, procedure, and MRI acquisition in Experiment 2 were identical to those described in Experiment 1.

4.2. fMRI preprocessing and statistical analysis

Data preprocessing and analysis was conducted using SPM8 (Wellcome Department of Cognitive Neurology, London). Preprocessing steps in Experiment 2 were identical to those described in Experiment 1.

Two types of statistical analyses were performed on this longitudinal dataset. First, we used the ROIs defined based on the whole-brain analysis [reward > loss] in the cross-sectional study (left VS, right VS, and medial PFC) to examine longitudinal changes in neural activation related to changes in behavior, age, pubertal development, and individual's reward sensitivity. Second, we performed a whole-brain analysis on the longitudinal dataset within the GLM framework, with a 2 (reward, loss) × 2 (T1, T2) repeated measures ANOVA (flexible factorial design). The latter analysis allowed for a whole-brain inspection of a main effect of outcome [reward > loss], a main effect of time [T2 > T1], and an interaction between the contrast [reward > loss] × time.

5. Results and discussion Experiment 2

5.1. Behavior

The proportion of plays in the adolescent longitudinal sample was .62 (*SD* = .13) for T1 and .63 (*SD* = .11) for T2. A correlational

analysis between T1 and T2 showed that proportion of plays was significantly correlated across sessions ($r = .41$, $p < .02$), however, this correlation also indicates there was a fair amount of within-individual differences in choice behavior across time.

A set of linear regressions with proportion of plays at each time point as a dependent and Age (continuous) at each time point as an independent variable showed that Age did not significantly predict behavior on T1 and T2 (respectively) nor did Age on T1 predict the change in behavior from T1–T2. Similarly, BAS subscales and PDS scores at T1 and T2 did not predict proportion of plays on T1 and T2 (respectively) nor predicted scores on T1 the change in behavior from T1–T2. (all p's > .05). Thus, risk-taking propensity was generally stable across time and was not related to developmental factors and individual differences.

5.2. ROI analyses

We extracted individual activation values for the longitudinal dataset from the ROI masks used in the cross-sectional whole-brain analysis and focused on the contrast [reward > loss] in left VS ($x = -16$, $y = 11$, $z = -5$), right VS ($x = 16$, $y = 11$, $z = -5$), and medial PFC ($x = -6$, $y = 55$, $z = 7$). These ROIs were chosen to enable comparison with Experiment 1. A repeated measures ANOVA was performed for each ROI with reward-related activation at T1 and T2. There was no effect of Time (i.e., Age) on brain activation in the VS and medial PFC. An additional correlational analysis for each ROI between reward-related activation at T1 and T2 showed no significant correlations over time within these ROIs.

We performed a linear regression [backward selection] with proportion of plays, PDS score, BAS scores, and IQ as independent and brain activation in an ROI [reward > loss] as a dependent variable. The same analysis was repeated with Age instead of PDS scores. These regression analyses were performed for behavioral scores and brain activation at T1, T2, and the change in behavioral scores and brain activation between T1 and T2.

The regression for medial PFC at T1 showed no significant results of any of these predictors. The regression analysis for left VS at T1 showed that BAS Fun-seeking score, Beta = .51, $p < .01$, and pubertal developmental score, Beta = .32, $p < .05$, were positively associated with left VS activation. A regression analysis for right VS at T1 showed that BAS Fun-seeking score was positively associated with right VS reward-related activation, Beta = .51, $p < .01$. A similar set of regressions for T2 showed no significant effects of Age, proportion of plays, PDS or BAS scores on reward-related brain activation at T2.

Crucially, regression analyses were performed with the *change* over time in reward-related activation in medial PFC, Right VS, and Left VS as dependent variables, and the *change* over time in proportion of plays, PDS score, and BAS scores as independent variables. The regression for medial PFC showed no significant results of any of these predictors. A regression for left VS showed that the change in BAS Fun-seeking score was positively associated with the change in reward-related activation in left VS, Beta = .38, $p < .05$. A regression for right VS showed that the change in BAS Fun-seeking score was positively associated with the change in reward-related activation in Right VS, Beta = .36, $p < .05$ (see Fig. 4).

These results suggest that an increased VS response to rewards is associated with increased self-reported fun seeking; this relationship is independent of developmental factors, such as age and pubertal development.

5.3. Whole-brain analysis

To ensure that the prespecified ROIs did not prevent us from observing brain regions that showed changes in activation over time when processing rewards compared to losses, we performed a whole-brain 2 (reward, loss) × 2 (T1, T2) repeated measures ANOVA (flexible factorial design) on the longitudinal dataset.

Results for the main effect of outcome [reward > loss] across all participants resulted in VS activation (right) and a cluster of activation in the medial PFC (see Fig. 5). Reward-related activation was also found in the PCC and visual cortex (see Supplementary Table 1 for regions of activation and their coordinates). No significant results were found for the opposite contrast [loss > reward]. The interaction term between reward-loss × time showed no significant results at FWE or more lenient corrected thresholds (FDR $p < .05$ and uncorrected $p < .001$).

Thus, even though correlations in ROI activation values indicate intra-individual variability in brain activation, there was a strong main effect of reward-related activation at the group level.

6. General discussion

The goal of this study was to examine stability, change, and individual differences in reward processing in adolescence. We first examined the relation between brain and behavior in the context of reward processing and risky decision-making. Second, we examined the effects of age, pubertal development, and reward sensitivity on reward-related brain activation in a cross-sectional and longitudinal comparison. To these ends, Experiment 1 utilized a risky decision task in a cross-sectional sample of adolescents and young adults. Experiment 2 was a longitudinal extension, in which an adolescent subset was re-studied using the same paradigm 2 years later.

For the current study, we used a task in which participants had the opportunity to *play* or *pass*. The advantage of this design is that rewards and losses are thought to be more meaningful when there is an active choice to play (Rao et al., 2008; Tricomi et al., 2004). Therefore, the analyses were focused on the brain responses to reward and loss following play trials. As expected, monetary rewards resulted in robust activation in the bilateral VS and medial PFC in the cross-sectional sample (Delgado, 2007; Knutson et al., 2001).

The longitudinal analysis confirmed these findings by revealing activation in a highly similar reward-related network including most predominantly VS and medial PFC. These activation patterns are in line with the functional roles of these regions, such as the coding of reward throughout various stages of decision making for the VS (Liu et al., 2007), and action regulation and control for the medial PFC (Ridderinkhof et al., 2004; Rushworth, Mars, & Summerfield, 2012). We, however, did not observe brain activation in a more ventral region of the medial PFC or the adjacent orbital frontal cortex. Given that these regions have been related to the representation and the comparison of value during risky choice (Kuhnen & Knutson, 2005; Rushworth et al., 2011), it may be that these regions are more readily activated in response to choice than outcome processing.

Interestingly, no results were found for the opposite contrast (i.e., loss > reward), suggesting that the brain regions involved in winning and losing overlap. This finding is supported by previous findings that also showed no results for the contrast no-gain versus gain in a similar design (e.g., Van Leijenhorst, Gunther Moor, et al., 2010). A possible explanation could be that in the current context negative feedback was not a learning signal and therefore there was no activation greater for loss than gain (Van Duijvenvoorde & Crone, 2013).

A whole-brain analysis showed that the propensity to play (i.e., to choose the risky option) was related to increased reward-related activation in both VS and medial PFC. That is, participants who generally played more often showed, as expected, increased activation in VS, but also increased activation in medial PFC after rewards compared to losses. Previous studies demonstrated that activation

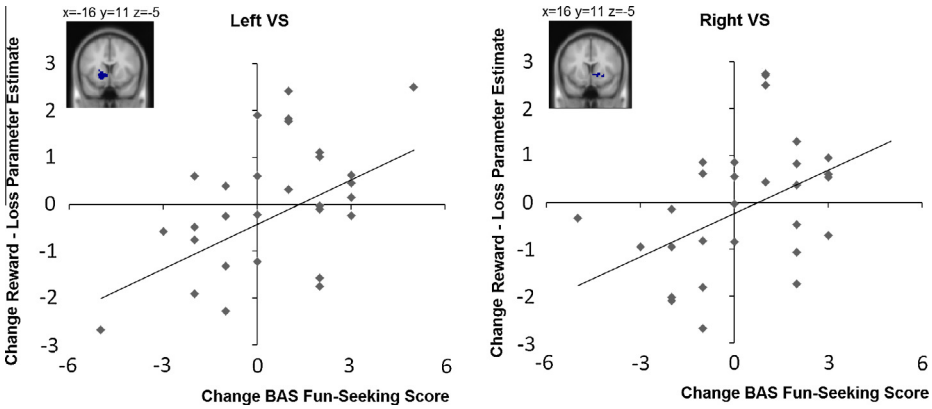

Fig. 4. Scatterplots for the change in reward > loss activation (T1–T2) and the change in left and right ventral striatum (VS) and self-reported Fun-seeking.

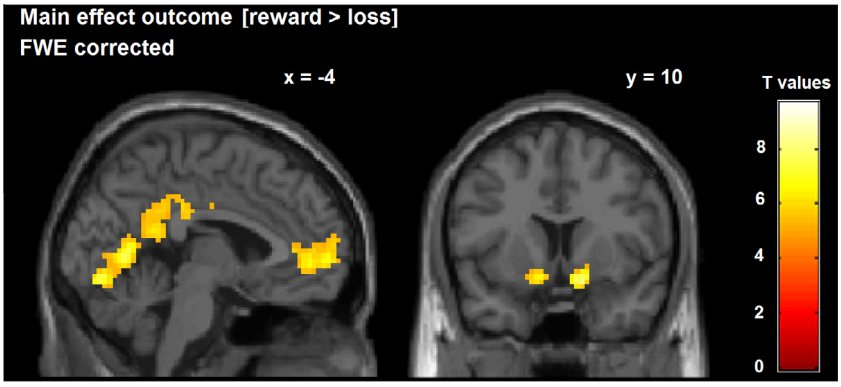

Fig. 5. Whole-brain results for the main effect of outcome [reward > loss] for all participants in T1 and T2 from a 2 × 2 flexible factorial ANOVA. Results are shown at an FWE-corrected threshold of $p < .05$, >10 contiguous voxels.

in medial PFC regions during decision-making was related to increased risk-taking tendencies (Van Leijenhorst, Gunther Moor, et al., 2010; Xue et al., 2009; but see Eshel, Nelson, Blair, Pine, & Ernst, 2007), which is consistent with its role in reward-related action tendencies (Rushworth et al., 2011; Rushworth et al., 2012). The current study extends previous findings by showing that medial PFC activation during outcome processing was positively related to the tendency to choose a risky option in a cross-sectional sample.

6.1. Developmental changes and individual differences

A current debate in the literature concerns the VS response to rewards in adolescence. Prior studies have reported both increases and decreases in mid-adolescence, although this may depend also on task demands (Bjork et al., 2010; Galvan, 2010; Richards, Plate, & Ernst, 2013). In a prior study by Op de Macks et al. (2011), which involved a subset of participants reported in this study, it was found that reward-related brain activation correlated positively with testosterone levels, in both boys and girls. This led us to hypothesize that reward-related activation would peak in mid-adolescence, as can be expected based on adolescent-typical changes in the dopamine system (Galvan, 2010; Luciana & Collins, 2012). However, a comparison with a sample of young adults (ages 18–25) did not show developmental differences related to age or puberty. Only at lower (uncorrected) thresholds, reward-related activation in left putamen increased linearly with age. Thus, these results report no direct evidence for a peak in adolescent VS activation and suggest that individual differences in adolescence may be more important.

Indeed, this study showed that reward responses in the VS were related to the extent to which participants reported to be fun seeking in everyday life. Previously, Galvan et al. (2007) reported that neural responses to rewards in adolescence could be partly explained by individual differences in risk-taking behavior in everyday life. It was previously reported in a large behavioral developmental study including 935 participants between ages 10 and 30 that self-reported sensation seeking peaks in mid-adolescence (Steinberg et al., 2008). Possibly, findings in prior studies of heightened VS activation in adolescents compared to adults were driven especially by risk-seeking adolescents. The current study provided further evidence for this hypothesis by showing that within individuals, changes in fun seeking over time correlated positively with changes in reward-related VS activation. This longitudinal extension provides a strong case for the role of individual differences in reward-seeking behavior, which may bias some adolescents to respond more strongly to rewards than others. Further study is needed to study how hyperactivity in VS is related to individuals' learning and decision-making.

6.2. Functional connectivity

The next question concerned whether there was functional connectivity between VS and medial PFC. In the current study a functional connectivity analysis in the cross-sectional sample indicated increased connectivity between VS and medial PFC after processing rewards compared to losses. Contrary to expectations we did not

find a relation between VS-medial PFC functional connectivity and task-related behavior (i.e., proportion of plays). Instead, increased functional connectivity was found between VS and insula after rewards compared to losses, and the strength of this functional connectivity was related to individuals' risky decision-making. That is, greater connectivity was associated with an attenuated tendency to play, suggesting a potentially regulatory role of the insula (see also Cho et al., 2012). Indeed, insula activation has been implicated in saliency detection (Menon & Uddin, 2010), harm avoidance (Paulus, Rogalsky, Simmons, Feinstein, & Stein, 2003), and risk processing (Mohr, Biele, & Heekeren, 2010). However, given the low number of trials in the current study, these results need to be interpreted carefully.

Previous work also indicated a relation between frontostriatal structural connections and choice behavior, in which higher integrity of frontostriatal white-matter tracts was associated with less impulsive choice behavior, suggesting that the PFC has a regulatory role over the VS (Peper et al., 2012). However, other findings demonstrated that more mature white-matter tracts in the frontal cortex (corpus callosum, connecting left and right prefrontal and orbital frontal cortex), is related to *increased* engagement in risky behaviors (Berns, Moore, & Capra, 2009). These mixed findings indicate the need to further study how frontostriatal connections influence risk taking in adolescence.

6.3. Limitations

There are a couple of critical aspects to take into account when reporting and comparing studies on risk and reward processing (Galvan, 2010). First, studies may differ in the component of the decision-making process targeted (e.g., decision-making, cue/anticipation, and outcome). Due to its task design the current study focused specifically on outcome processing. However, future studies may profit from analyzing both decision-related and outcome-related responses (see also Barkley-Levenson, Van Leijenhorst, & Galvan, 2013; Paulsen et al., 2012; Van Leijenhorst, Gunther Moor, et al., 2010). Also, the current task was not aimed toward decomposing influences of risk, expected value, and reward that may drive individuals' decision making. Combinations in future paradigms will be valuable to further disentangle these components of decision-making.

Second, it is important to consider the task contrast and/or baseline used across studies. That is, while this study used a typical contrast of reward versus loss, future studies may benefit from a neutral baseline (e.g., including a neutral condition) to distinguish whether differences in reward processing are due to differences in the brain responses to reward or responses to loss. Alternatively, parametric modulation of rewards and losses (e.g. Tom et al., 2007; Xue et al., 2009) may be a promising approach in distinguishing reward versus loss-related activation across development.

Third, even though the current longitudinal sample is an important starting point, the sample size is relatively small for detecting subtle developmental changes. We aimed to present these data as evidence that change scores are informative for understanding developmental patterns. In future studies, larger sample sizes will allow us to make stronger inferences about developmental trajectories. Related, the relative low number of trials for each contrast (i.e., on average, 17 reward and 17 loss trials) could hinder the detection of age-related changes. While previous fMRI studies reported developmental changes in reward processing based on similar numbers of trials per condition (i.e., 18 trials per condition; Bjork et al., 2004; Ernst et al., 2005), these studies included more than two conditions, suggesting the need for a larger number of trials in future studies.

Finally, task context may be driving age-related changes in risk-taking or brain activation. For instance, a recent study suggested that adolescents may be more ambiguity-tolerant, instead of more risk-tolerant compared to adults, indicating they are more likely to take a risk under conditions of unknown probabilities (i.e., an 'ambiguous' decision–situation) compared to known probabilities (i.e., a 'risky' decision–situation) (Tymula et al., 2012). Future studies are important for disentangling adolescent sensitivities across different decision contexts, such as risky, ambiguous, or social decision contexts.

6.4. Conclusion

In the current study, we used a risky decision task to investigate neurodevelopmental changes (cross-sectional and longitudinal) in the processing of rewards and its relation to task-related behavior (i.e., the proportion of play choices), age, pubertal development, and individuals' reward sensitivity. Adolescence is characterized as a period of increased reward sensitivity and risk taking, but it remains unclear whether changes in reward-related brain activation drive the changes in risk-taking behavior. The results of the experiments reported here advance our understanding of the potential mechanisms underlying reward processing and risky decision-making in adolescence. Specifically, these results indicated that increased activation within a network of brain regions responsive to rewards—including VS and medial PFC—is related to an increased tendency to play and heightened self-reported fun seeking. Longitudinal comparisons confirmed the association between VS activation and individual's fun seeking. Furthermore, we observed increased connectivity between VS and medial PFC after rewards versus losses, but only the increased functional connectivity between VS and insula was associated with attenuated risky decision-making. Future challenges lie in unraveling how localized brain activation and frontostriatal connections are related to changes in risk taking across adolescence and in creating paradigms that are sensitive to individual and developmental differences in risk-taking tendencies.

Acknowledgement

The authors would like to thank Wouter van den Bos for his help with functional connectivity analyses.

Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bandc.2 013.10.005.

References

Barkley-Levenson, E. E., Van Leijenhorst, L., & Galvan, A. (2013). Behavioral and neural correlates of loss aversion and risk avoidance in adolescents and adults. *Developmental Cognitive Neuroscience, 3*, 72–83. http://dx.doi.org/10.1016/j.dcn.2012.09.007.

Beaver, J. D., Lawrence, A. D., Van Ditzhuijzen, J., Davis, M. H., Woods, A., & Calder, A. J. (2006). Individual differences in reward drive predict neural responses to images of food. *Journal of Neuroscience, 26*, 5160–5166. http://dx.doi.org/10.1523/JNEUROSCI.0350-06.2006.

Berns, G. S., Moore, S., & Capra, C. M. (2009). Adolescent engagement in dangerous behaviors is associated with increased white matter maturity of frontal cortex. *PLoS ONE, 4*, e6773. http://dx.doi.org/10.1371/journal.pone.0006773.

Bjork, J. M., Knutson, B., Fong, G. W., Caggiano, D. M., Bennett, S. M., & Hommer, D. W. (2004). Incentive-elicited brain activation in adolescents: Similarities and differences from young adults. *Journal of Neuroscience, 24*, 1793–1802. http://dx.doi.org/10.1523/JNEUROSCI.4862-03.2004.

Bjork, J. M., Knutson, B., & Hommer, D. W. (2008). Incentive-elicited striatal activation in adolescent children of alcoholics. *Addiction, 103*, 1308–1319. http://dx.doi.org/10.1111/j.1360-0443.2008.02250.x.

Bjork, J. M., Smith, A. R., Chen, G., & Hommer, D. W. (2010). Adolescents, adults and rewards: Comparing motivational neurocircuitry recruitment using fMRI. *PLoS ONE, 5*, e11440. http://dx.doi.org/10.1371/journal.pone.0011440.

Brett, M. C., Anton, J.-L., Valabregue, R., & Poline, J.-B. (2002). Region of interest analysis using an SPM toolbox. *NeuroImage, 16*, 497.

Blakemore, S. J., Burnett, S., & Dahl, R. E. (2010). The role of puberty in the developing adolescent brain. *Human Brain Mapping, 31*, 926–933. http://dx.doi.org/10.1002/hbm.21052.

Blakemore, S. J., & Robbins, T. W. (2012). Decision-making in the adolescent brain. *Nature Reviews Neuroscience, 15*, 1184–1191. http://dx.doi.org/10.1038/nn.3177.

Buckholtz, J. W., Treadway, M. T., Cowan, R. L., Woodward, N. D., Benning, S. D., Li, R., et al. (2010). Mesolimbic dopamine reward system hypersensitivity in individuals with psychopathic traits. *Nature Neuroscience, 13*, 419–421. http://dx.doi.org/10.1038/nn.2510.

Cho, Y. T., Fromm, S., Guyer, A. E., Detloff, A., Pine, D. S., Fudge, J. L., et al. (2012). Nucleus accumbens, thalamus and insula connectivity during incentive anticipation in typical adults and adolescents. *NeuroImage, 66C*, 508–521. http://dx.doi.org/10.1016/j.neuroimagae.2012.10.013.

Clark, L., Lawrence, A. J., Astley-Jones, F., & Gray, N. (2009). Gambling near-misses enhance motivation to gamble and recruit win-related brain circuitry. *Neuron, 61*, 481–490. http://dx.doi.org/10.1016/j.neuron.2008.12.031.

Carver, C. S., & White, T. L. (1994). Behavioral inhibition, behavioral activation, and affective responses to impending reward and punishment: The BIS/BAS scales. *Journal of Personality and Social Psychology, 67*, 319–333.

Cocosco, C. A., Kollokian, V., Kwan, R. K. S., & Evans, A. C. (1997). Brain web: Online interface to a 3D MRI simulated brain database. *NeuroImage, 5*, S452.

Cohen, J. R., Asarnow, R. F., Sabb, F. W., Bilder, R. M., Bookheimer, S. Y., Knowlton, B. J., et al. (2010). A unique adolescent response to reward prediction errors. *Nature Neuroscience, 13*, 669–671. http://dx.doi.org/10.1038/nn.2558.

Cohen, M. X., Bour, L., Mantione, M., Figee, M., Vink, M., Tijssen, M. A. J., et al. (2012). Top-down directed synchrony from medial frontal cortex to nucleus accumbens during reward anticipation. *Human Brain Mapping, 33*, 246–252. http://dx.doi.org/10.1002/hbm.21195.

Dahl, R. E. (2004). Adolescent brain development: A period of vulnerabilities and opportunities. Keynote address. *Annals of the New York Academy of Sciences, 1021*, 1–22. http://dx.doi.org/10.1196/annals.1308.001.

De Water, E., Braams, B. R., Crone, E. A., & Peper, J. (2013). Pubertal maturation and sex steroids are related to alcohol use in adolescents. *Hormones and Behavior, 63*, 392–397. http://dx.doi.org/10.1016/j.yhbeh.2012.11.018.

Delgado, M. R. (2007). Reward-related responses in the human striatum. *Annals of the New York Academy of Sciences, 1104*, 70–88. http://dx.doi.org/10.1196/annals.1390.002.

Ernst, M., & Fudge, J. L. (2009). A developmental neurobiological model of motivated behavior: Anatomy, connectivity and ontogeny of the triadic nodes. *Neuroscience and Biobehavioral Reviews, 33*, 367–382. http://dx.doi.org/10.1016/j.neubiorev.2008.10.009.

Ernst, M., Nelson, E. E., Jazbec, S., McClure, E. B., Monk, C. S., Leibenluft, E., et al. (2005). Amygdala and nucleus accumbens in responses to receipt and omission of gains in adults and adolescents. *NeuroImage, 25*, 1279–1291. http://dx.doi.org/10.1016/j.neuroimage.2004.12.038.

Eshel, N., Nelson, E. E., Blair, J. R., Pine, D. S., & Ernst, M. (2007). Neural substrates of choice selection in adults and adolescents: Development of the ventrolateral prefrontal and anterior cingulate cortices. *Neuropsychologia, 45*, 1270–1279. http://dx.doi.org/10.1016/j.neuropsychologia.2006.10.004.

Forbes, E. E., Ryan, N. D., Phillips, M. L., Manuck, S. B., Worthman, C. M., Moyles, D. L., et al. (2010). Healthy adolescents' neural response to reward: Associations with puberty, positive affect, and depressive symptoms. *Journal of the American Academy of Child and Adolescent Psychiatry, 49*, 162–172.

Friston, K. J., Buechel, C., Fink, G. R., Morris, J., Rolls, E., & Dolan, R. J. (1997). Psychophysiological and modulatory interactions in neuroimaging. *NeuroImage, 6*, 218–229. http://dx.doi.org/10.1006/nimg.1997.0291.

Galvan, A. (2010). Adolescent development of the reward system. *Frontiers in Human Neuroscience, 4*, 1–9. http://dx.doi.org/10.3389/neuro.09.006.2010.

Galvan, A., Hare, T. A., Davidson, M., Spicer, J., Glover, G., & Casey, B. J. (2005). The role of ventral frontostriatal circuitry in reward-based learning in humans. *Journal of Neuroscience, 25*, 8650–8656. http://dx.doi.org/10.1523/JNEUROSCI.2431-05.2005.

Galvan, A., Hare, T. A., Parra, C. E., Penn, J., Voss, H., Glover, G., et al. (2006). Earlier development of the accumbens relative to orbitofrontal cortex might underlie risk-taking behavior in adolescents. *Journal of Neuroscience, 26*, 6885–6892. http://dx.doi.org/10.1523/JNEUROSCI.1062-06.2006.

Galvan, A., Hare, T., Voss, H., Glover, G., & Casey, B. J. (2007). Risk-taking and the adolescent brain: Who is at risk? *Developmental Science, 10*, F8–F14. http://dx.doi.org/10.1111/j.14677687.2006.00579.

Gunther Moor, B., Op de Macks, Z., Güroğlu, B., Rombouts, S. A. R. B., Van der Molen, M. W., & Crone, E. A. (2012). Neurodevelopmental changes of reading the mind in the eyes. *Social Cognitive and Affective Neuroscience, 7*, 44–52. http://dx.doi.org/10.1093/scan/nsr020.

Haber, S. N., & Knutson, B. (2010). The reward circuit: Linking primate anatomy and human imaging. *Neuropsychopharmacology, 35*, 4–26. http://dx.doi.org/10.1038/npp.2009.129.

Kennerley, S. W., & Walton, M. E. (2011). Decision making and reward in frontal cortex: Complementary evidence from neurophysiological and neuropsychological studies. *Behavioral Neuroscience, 125*, 297–317. http://dx.doi.org/10.1037/a0023575.

Knutson, B., Fong, G. W., Adams, C. M., Varner, J. L., & Hommer, D. (2001). Dissociation of reward anticipation and outcome with event-related fMRI. *NeuroReport, 12*, 3683–3687.

Kuhnen, C. M., & Knutson, B. (2005). The neural basis of financial risk taking. *Neuron, 47*, 763–770. http://dx.doi.org/10.1016/j.neuron.2005.08.008.

Liu, X., Powell, D. K., Wang, H., Gold, B. T., Corbly, C. R., & Joseph, J. E. (2007). Functional dissociation in frontal and striatal areas for processing of positive and negative reward information. *Journal of Neuroscience, 27*, 4587–4597. http://dx.doi.org/10.1523/JNEUROSCI.5227-06.2007.

Luciana, M., & Collins, P. F. (2012). Incentive motivation, cognitive control, and the adolescent brain: Is it time for a paradigm shift? *Child Development Perspectives, 6*, 392–399. http://dx.doi.org/10.1111/j.1750-8606.2012.00252.x.

May, J. C., Delgado, M. R., Dahl, R. E., Stenger, V. A., Ryan, N. D., Fiez, J. A., et al. (2004). Event-related functional magnetic resonance imaging of reward-related brain circuitry in children and adolescents. *Biological Psychiatry, 55*, 359–366.

McKell Carter, R., Meyer, J. R., & Huettel, S. A. (2010). Functional neuroimaging of intertemporal choice models: A review. *Journal of Neuroscience, Psychology and Economics, 3*, 27–45. http://dx.doi.org/10.1037/a0018046.

Menon, V., & Uddin, L. Q. (2010). Saliency, switching, attention and control: A network model of insula function. *Brain Structure and Function, 214*, 655–667. http://dx.doi.org/10.1007/s00429-010-0262-0.

Mohr, P. N., Biele, G., & Heekeren, H. R. (2010). Neural processing of risk. *Journal of Neuroscience, 30*, 6613–6619. http://dx.doi.org/10.1523/JNEUROSCI.0003-10.2010.

Nelson, E. E., Leibenluft, E., McClure, E. B., & Pine, D. S. (2005). The social re-orientation of adolescence: A neuroscience perspective on the process and its relation to psychopathology. *Psychological Medicine, 35*, 163–174. http://dx.doi.org/10.1017/S0033291704003915.

Op de Macks, Z. A., Gunther Moor, B., Overgaauw, S., Güroğlu, B., Dahl, R. E., & Crone, E. A. (2011). Testosterone levels correspond with increased ventral striatum activation in response to monetary rewards in adolescents. *Developmental Cognitive Neuroscience, 1*, 506–516. http://dx.doi.org/10.1016/j.dcn.2011.06.003.

Padmanabhan, A., Geier, C. F., Ordaz, S. J., Teslovich, T., & Luna, B. (2011). Developmental changes in brain function underlying the influence of reward processing on inhibitory control. *Developmental Cognitive Neuroscience, 1*, 517–529. http://dx.doi.org/10.1016/j.dcn.2011.06.004.

Paulsen, D. J., McKell Carter, R., Platt, M. L., Huettel, S. A., & Brannon, E. M. (2012). Neurocognitive development of risk aversion from early childhood to adulthood. *Frontiers in Human Neuroscience, 5*, 178. http://dx.doi.org/10.3389/fnhum.2011.00178.

Paulus, M. P., Rogalsky, C., Simmons, A., Feinstein, J. S., & Stein, M. B. (2003). Increased activation in the right insula during risk-taking decision making is related to harm avoidance and neuroticism. *NeuroImage, 19*, 1439–1448. http://dx.doi.org/10.1016/S1053-8119(03)00251-9.

Peper, J. S., Mandl, R. C. W., Braams, B. R., de Water, E., Heijboer, A. C., Koolschijn, P. C. M. P., et al. (2012). Delay discounting and frontostriatalfiber tracts: A combined DTI and MTR study on impulsive choices in healthy young adults. *Cerebral Cortex*. http://dx.doi.org/10.1093/cercor/bhs163 (epub ahead of print).

Petersen, A. C., Crockett, L., Richards, M., & Boxer, A. (1988). A self-report measure of pubertal status: Reliability, validity, and initial norms. *Journal of Youth and Adolescence, 17*, 117–133. http://dx.doi.org/10.1007/BF01537962.

Rao, H., Korczykowski, M., Pluta, J., Hoang, A., & Detre, J. A. (2008). Neural correlates of voluntary and involuntary risk taking in the human brain: An fMRI study of the balloon analog risk task (BART). *NeuroImage, 42*, 902–910. http://dx.doi.org/10.1016/j.neuroimage.2008.05.046.

Richards, J., Plate, R. C., & Ernst, M. (2013). A systematic review of fMRI reward paradigms used in studies of adolescents vs. adults: The impact of task design and implications for understanding neurodevelopment. *Neuroscience and Biobehavioral Reviews, 37*, 976–991. http://dx.doi.org/10.1016/j.neubiorev.2013.03.004.

Ridderinkhof, K. R., Ullsperger, M., Crone, E. A., & Nieuwenhuis, S. (2004). The role of the medial frontal cortex in cognitive control. *Science, 306*, 443–447.

Rushworth, M., Mars, R. B., & Summerfield, C. (2012). General mechanisms for making decisions? *Current Opinion in Neurobiology, 19*, 75–83. http://dx.doi.org/10.1016/j.conb.2009.02.005.

Rushworth, M., Noonan, M. P., Boorman, E. D., Walton, M. E., & Behrens, T. E. (2011). Frontal cortex and reward-guided learning and decision-making. *Neuron, 70*, 1054–1069. http://dx.doi.org/10.1016/j.neuron.2011.05.014.

Sisk, C. L., & Zehr, J. L. (2005). Pubertal hormones organize the adolescent brain and behavior. *Frontiers in Neuroendocrinology, 26*, 163–174. http://dx.doi.org/10.1016/j.yfrne.2005.10.003.

Somerville, L. H., Jones, R. M., & Casey, B. J. (2010). A time of change: Behavioral and neural correlates of adolescent sensitivity to appetitive and aversive environmental cues. *Brain and Cognition, 72*, 124–133. http://dx.doi.org/10.1016/j.bandc.2009.07.003.

Steinberg, L., Albert, D., Cauffman, E., Banich, M., Graham, S., & Woolard, J. (2008). Age differences in sensation seeking and impulsivity as indexed by behavior and self report: Evidence for a dual system model. *Developmental Psychobiology, 44*, 1764–1778. http://dx.doi.org/10.1037/a0012955.

Tom, S. M., Fox, C. R., Trepel, C., & Poldrack, R. A. (2007). The neural basis of loss aversion in decision-making under risk. *Science, 315*, 515–518. http://dx.doi.org/10.1126/science.1134239.

Tricomi, E. M., Delgado, M. R., & Fiez, J. A. (2004). Modulation of caudate activity by action contingency. *Neuron, 41*, 281–292. http://dx.doi.org/10.1016/S0896-6273(03)00848-1.

Tymula, A., Rosenberg Belmaker, L. A., Roy, A. K., Ruderman, L., Manson, K., Glimcher, P. W., et al. (2012). Adolescents' risk-taking behavior is driven by tolerance to ambiguity. *PNAS, 109*, 17135–17140. http://dx.doi.org/10.1073/pnas.1207144109.

Van den Bos, W., Cohen, M. X., Kahnt, T., & Crone, E. A. (2012). Striatum-medial prefrontal cortex connectivity predicts developmental changes in reinforcement learning. *Cerebral Cortex, 22*, 1247–1255. http://dx.doi.org/10.1093/cercor/bhr198.

Van Duijvenvoorde, A. C. K., & Crone, E. A. (2013). A neuroeconomic approach to adolescent decision-making. *Current Directions in Psychological Science, 22*, 108–113. http://dx.doi.org/10.1177/0963721413475446.

Van Leijenhorst, L., Moor, B. G., Op de Macks, Z. A., Rombouts, S. A., Westenberg, P. M., & Crone, E. A. (2010). Adolescent risky decision-making: Neurocognitive development of reward and control regions. *NeuroImage, 51*, 345–355. http://dx.doi.org/10.1016/j.neuroimage.2010.02.038.

Van Leijenhorst, L., Zanolie, K., Van Meel, C. S., Westenberg, P. M., Rombouts, S. A. R. B., & Crone, E. A. (2010). What motivates the adolescent? Brain regions mediating reward sensitivity across adolescence. *Cerebral Cortex, 20*, 61–69. http://dx.doi.org/10.1093/cercor/bhp078.

Wechsler, D. (1991). *Wechsler intelligence scale for children—Manual* (3rd ed.). San Antonio: The Psychological Corporation.

Wechsler, D. (1997). *Wechsler adult intelligence scale—Administration and scoring manual* (3rd ed.). San Antonio: The Psychological Corporation.

Xue, G., Lu, Z., Levin, I. P., Weller, J. A., Li, X., & Bechara, A. (2009). Functional dissociations of risk and reward processing in the medial prefrontal cortex. *Cerebral Cortex, 19*, 1019–1027. http://dx.doi.org/10.1093/cercor/bhn147.

Yu, R., Branje, S. J. T., Keijsers, L., & Meeus, W. H. J. (2011). Psychometric characteristics of Carver and White's BIS/BAS scales in Dutch adolescents and their mothers. *Journal of Personality Assessment, 93*, 500–507. http://dx.doi.org/10.1080/00223891.2011.595745.