doi:10.1093/scan/nsv007 SCAN (2015) 10, 1219–1227

Individual differences in sensitivity to reward and punishment and neural activity during reward and avoidance learning

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In this functional neuroimaging study, we investigated neural activations during the process of learning to gain monetary rewards and to avoid monetary loss, and how these activations are modulated by individual differences in reward and punishment sensitivity. Healthy young volunteers performed a reinforcement learning task where they chose one of two fractal stimuli associated with monetary gain (reward trials) or avoidance of monetary loss (avoidance trials). Trait sensitivity to reward and punishment was assessed using the behavioral inhibition/activation scales (BIS/BAS). Functional neuroimaging results showed activation of the striatum during the anticipation and reception periods of reward trials. During avoidance trials, activation of the dorsal striatum and prefrontal regions was found. As expected, individual differences in reward sensitivity were positively associated with activation in the left and right ventral striatum during reward reception. Individual differences in sensitivity to punishment were negatively associated with activation in the left dorsal striatum during avoidance anticipation and also with activation in the right lateral orbitofrontal cortex during receiving monetary loss. These results suggest that learning to attain reward and learning to avoid loss are dependent on separable sets of neural regions whose activity is modulated by trait sensitivity to reward or punishment.

Keywords: reward; avoidance; striatum; orbitofrontal; reward sensitivity; punishment sensitivity

INTRODUCTION

The ability of individuals to acquire knowledge that allows them to maximize rewards and avoid punishment is referred to as reinforcement learning. Previous neuroimaging studies of reinforcement learning have identified the midbrain, striatum, amygdala, orbitofrontal and medial prefrontal cortex (BA 10, 32) as key neural regions involved in learning from reward (Gottfried *et al.*, 2002, 2003; McClure *et al.*, 2004; O'Doherty, 2004; Knutson and Cooper, 2005). However, the neural substrates involved in learning to avoid punishment have received lesser attention, and the available evidence suggests that the neural correlates of reward and punishment-related learning have important differences. For example, reward-based learning has been associated with increased activation in the striatum, amygdala and medial OFC, whereas punishment-based learning has been associated with greater activation in the insula or lateral OFC (O'Doherty *et al.*, 2001; Gottfried *et al.*, 2002; Wächter *et al.*, 2009; Elliott *et al.*, 2010).

Reinforcement learning is dependent on the rewarding value of outcomes and learned expectations of outcomes. These two factors are reflected in temporally separate phases of reinforcement learning, namely, anticipation and reception phases. The anticipation phase of reinforcement learning refers to the phase in which the organism responds to predictive cues of outcomes, whereas the reception phase refers to the phase in which reinforcing outcomes elicit a response. These two phases have been suggested to have different neurobiological bases (Berridge and Robinson, 1998; Baldo and Kelley, 2007). Functional neuroimaging studies have shown that anticipation of reward is associated with increased activation in the ventral striatum and anterior cingulate, whereas reward reception is associated with activations in the medial prefrontal cortex (PFC) and orbitofrontal cortex (Dillon *et al.*, 2008; Schott *et al.*, 2008; Hsu *et al.*, 2009; Rademacher *et al.*, 2010). The striatum has been found to be inconsistently activated across studies of reward reception (Knutson *et al.*, 2003; Bjork *et al.*, 2004; Dillon *et al.*, 2008). The majority of studies that have examined differences in the neural correlates associated with the anticipation and reception phases of reinforcement learning have been conducted within the context of learning to gain reward, whereas there is relatively little corresponding evidence from learning to avoid loss or punishment.

Individuals vary considerably in their sensitivity to reward and punishment (Carver and White, 1994). Sensitivity to reward refers to the degree to which an individual's behavior is motivated by reward-relevant stimuli and is believed to be regulated by the behavioral activation system (BAS), whereas sensitivity to punishment refers to the degree to which an individual's behavior is inhibited by punishment-relevant stimuli and is believed to be regulated by the behavioral inhibition system (BIS) (Gray, 1987; Gray and McNaughton, 2000). Abnormal sensitivity of BIS and BAS systems has been widely used to explain various behavioral and psychopathological problems such as conduct disorder, antisocial personality, depression, anxiety and attention deficit hyperactivity disorder (Quay, 1993; Johnson *et al.*, 2003). More recently, attention has focused on understanding of the neural bases of the BIS and BAS systems, especially in relation to in reinforcement learning. For example, Simon *et al.* (2010) conducted a functional magnetic resonance imaging (fMRI) study in which they asked participants to choose a designated correct target stimulus from two stimulus alternatives in order to win monetary reward. Participants' BAS sensitivity was positively correlated with neural activation in the ventral striatum during the receipt of monetary reward (Simon *et al.*, 2010). Similarly, Linke *et al.* (2010) reported that individuals with a greater level of self-reported motivation towards external rewards (such as money or social reputation) showed greater fMRI activation in the striatum and medial PFC while learning to choose a correct card from among two alternatives in order to receive greater monetary

Received 20 May 2014; Revised 14 October 2014; Accepted 9 February 2015
Advance Access publication 12 February 2015
This work was supported by the National Research Foundation of Korea (NRF) grant funded by the Ministry of Education, Science and Technology, the Republic of Korea (2012R1A2A2A01012159).
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reward (Linke *et al.*, 2010). Although accumulating evidence suggests that individual differences in sensitivity to reward may modulate striatal activation during reinforcement learning, what remains relatively unclear was whether this modulation effect is specific to types of reinforcement learning (reward *vs* avoidance) or to phases of learning (anticipation *vs* reception). These studies are helpful not only in elucidating neural bases of psychopathological disorders in relation to abnormal reward-processing but also in understanding a normal range of individual difference characteristics regarding neural bases of appetitive and aversive motivation.

The goal of the current fMRI study was to investigate how individual differences in sensitivity to reward and punishment modulate neural activations in brain regions involved in reinforcement learning. We examined two temporally distinct phases (anticipation and reception) and two separate types (reward gain and loss avoidance) of reinforcement learning. Healthy young volunteer participants were scanned using fMRI during a task in which participants learned to choose a target stimulus (a particular fractal pattern) between two alternative stimulus choices. Two different types of learning trials were presented. During reward trials, participants learned to choose a fractal stimulus in order to win money. During avoidance trials they learned to choose a fractal stimulus to avoid losing money. Two types of neutral trials devised to serve as separate baselines for the reward and avoidance trials were also presented. All trials required that participants press a key to indicate their selection of fractal pairs. Previous research has overt response production as an important task element in characterizing how the relevant neural systems code for reward values (Guitart-Masip *et al.*, 2012, 2014). Outside the scanner, sensitivity to reward and punishment was assessed using the behavioral inhibition/behavioral activation scales (BIS/BAS) (Carver and White, 1994). Based on the prior neuroimaging literature, we expected to find activation in the ventral striatum associated with reward learning, and that the amount of activation in the ventral striatum would be associated with individual differences in sensitivity to reward as assessed by the BAS. We also predicted that individual differences in sensitivity to punishment would be associated with activation in the insula and lateral OFC during avoidance learning.

METHOD

Participants

Nineteen healthy volunteers (10 males, age: 25.50 ± 2.99; 9 females, age 23.44 ± 1.66) were recruited from the local community through advertisements. Participants were all college students who reported no past or current diagnosis of neurological and psychiatric disorders. All participants were right-handed according to the Edinburgh Handedness Inventory (Oldfield, 1971). Participants gave written informed consent prior to the participation after the nature of the procedure was fully explained. This study was performed in accordance with the Declaration of Helsinki and the procedures were approved by the institutional review board of Korea University. Participants were monetarily compensated for their time.

Stimuli and task

On each experimental trial one of four different pairs of fractal stimuli was randomly presented for 1500 ms and the participant's task was to choose one of the fractals in the pair (Figure 1A). Each pair was specifically associated with one of four different trial conditions: Reward, Avoidance, Neutral R and Neutral A. In the Reward trial condition, choosing one of the fractals resulted in monetary gain with a 60% probability (High reward), and choosing the other in the pair resulted in monetary gain with a 30% probability (Low reward). In the

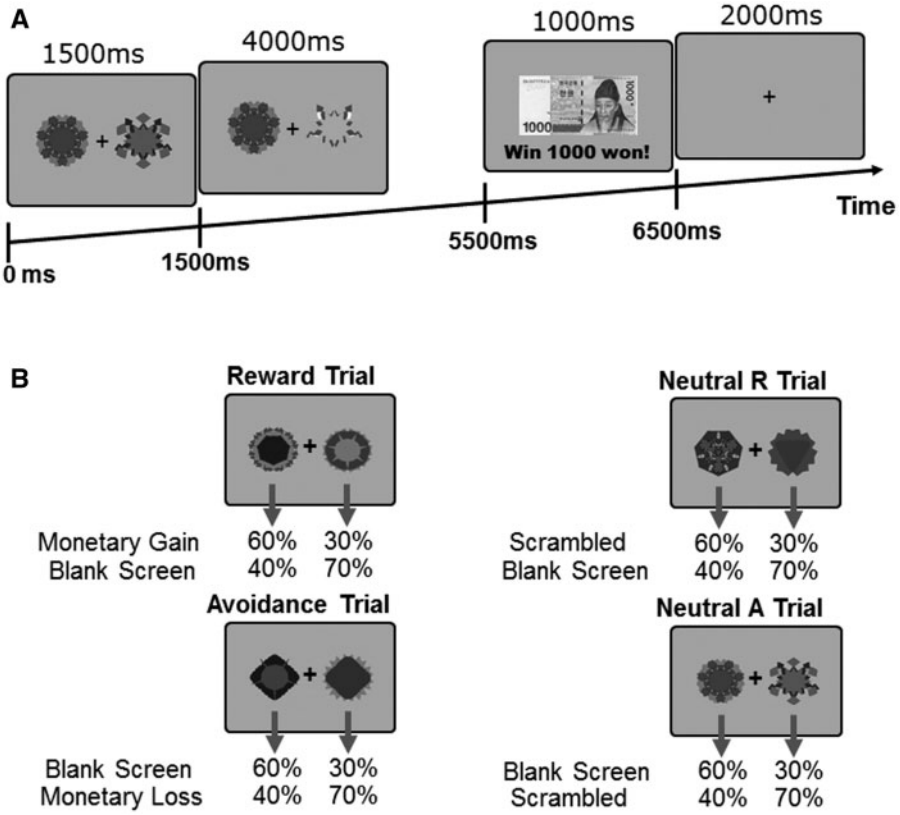

Fig. 1 Experimental task and timing of each event (**A**), and probabilities of monetary reward and loss associated with each fractal across different types of learning trials (**B**).

Avoidance trial condition, choosing one of the fractals resulted in avoidance of monetary loss with a 60% probability (High avoidance), and choosing the other in the pair resulted in avoidance of monetary loss with a 30% probability (Low avoidance). Two different types of neutral control conditions were used as in the previous study (Kim *et al.*, 2006) to control for motor responses and simple visual effects distinctively associated with reward and avoidance trials. That is, during reward trials, advantageous (rewarding) outcomes were associated with the presentation of feedback (i.e. a picture of money), whereas during avoidance trials, advantageous outcomes were associated with the absence of loss feedback (i.e. a blank screen). In the Neutral R condition which served the baseline for reward trials, each fractal was associated with either a 60 or 30% probability of obtaining neutral feedback (i.e. a scrambled picture of money). In the Neutral A condition which served as the baseline for avoidance trials, each fractal was associated with either a 60 or 30% probability of receiving no feedback (i.e. a blank screen); otherwise, they received neutral feedback of a scrambled picture of money.

In each trial, once a fractal had been selected, it slightly increased in brightness for 4000 ms and was followed by visual feedback for 1000 ms indicating either a reward (a picture of a money bill with text below saying 'You win 1000 won'), an aversive outcome (a red cross overlying a picture of a money bill with text below saying 'You lost 1000 won'), neutral feedback (a scrambled picture of a bill with text below saying 'No change'), or no feedback (a blank screen with a crosshair in the center, meaning no monetary change) (Figure 1B). Finally, a fixation cross was presented for 2000 ms before the next trial began. Prior to scanning, participants completed several practice trials to familiarize them with the task procedures. Participants were explicitly informed that depending on their choices on each trial they might gain money, lose money, or neither gain or lose money. They were also told that the monetary feedback would be summed throughout the task and their cumulative performance would determine the amount of monetary incentives in the range of 0–5000 KRW (~5 USD) that they would receive at the end of the experiment. To maximize their monetary reward, participants were instructed to try as much as possible to maximize their final monetary balance. However, all participants in fact received the same maximum reward 5000 KRW at the end of the experiment, in addition to their monetary compensation for participation in the study. Participants completed two ~20-min scanning runs, each consisting of 120 trials (30 trials per condition × 4 conditions). The presentation order of all four conditions was intermixed in a pseudorandom manner across the runs, and the specific assignment of fractal pairs to a given trial type was fully counterbalanced across participants.

Assessment of behavioral inhibition/behavioral activation scale

Participants completed a Korean version of the BIS/BAS scale (Kim and Kim, 2001). This self-reported questionnaire was originally proposed by Carver and White (1994) and includes three subscales (Drive, Reward Responsiveness and Fun Seeking) that together form the BAS scale and the BIS scale. The mean scores for the participants were 33.94 (s.d., 5.38) for the BAS and 16.22 (s.d., 3.65) for the BIS. No significant correlation between the BIS and BAS scales were observed ($r = 0.001$, *ns*).

Imaging data acquisition

Images were acquired at the Korea University Brain Imaging Center using a 3T Siemens Trio scanner (Siemens Medical Solutions, Germany). A high-resolution T_1-weighed whole-brain anatomical scan (1 mm^3 voxel resolution, magnetization-prepared rapid acquisition with gradient echo) was acquired prior to functional imaging. Functional brain images during the task were acquired in 36 axial slices using an echo planar imaging pulse sequence, with a TR of 2000 ms, a TE of 30 ms, a flip angle of 90°, a field of view of 240 × 240 mm^2, matrix size = 64 × 64 and slice thickness = 4 mm with no gap. The stimuli were presented on a computer screen using fMRI-compatible video goggles (Nordic Neurolab, Bergen, Norway). Responses were made via a fiber optic button box (Current Designs, Philadelphia, PA).

Imaging data analysis

Image preprocessing and statistical analyses were performed using SPM8 (http://www.fil.ion.ucl.ac.uk/spm). Functional images were realigned to the first volume to correct for head motion, co-registered to the T1-weighted structural image, spatially normalized to the MNI space (Montreal Neurological Institute, Canada), resampled to 2 × 2 × 2 mm voxels and smoothed with a Gaussian kernel of a full-width at half-maximum of 8 mm. Functional images were analysed using a general linear model (Friston *et al.*, 1995) for event-related designs. Blood oxygen level dependent (BOLD) hemodynamic responses were modeled for four anticipation periods (Reward, Avoidance, Neutral R and Neutral A; modeled across 0-4 s after fractal selection), and eight reception epochs (rewarded reward trials, unrewarded reward trials, punished avoidance trials, unpunished avoidance trials, scrambled neutral R trials, fixation neutral R trials, scrambled neutral A trials, fixation neutral A trials; modeled across 0–3 s after outcome feedback).

The following linear contrasts of interest between conditions were calculated for each individual participant's BOLD response parameter estimates (beta weights): (i) reward anticipation (Reward trials—Neutral R trials), (ii) avoidance anticipation (Avoidance trials—Neutral A trials), (iii) reward reception (rewarded/Reward trials—scramble feedback/Neutral R trials), (iv) no reward (unrewarded/Reward trials—no feedback/Neutral R trials), (v) loss avoidance (unpunished/Avoidance trials—no feedback/Neutral A trials) and (vi) loss reception (punished/Avoidance trials—scramble feedback/Neutral A trials). Each of these parameter estimate contrasts was then entered into second-level mixed effects analyses with subjects as the random factor, and one-sample *t*-tests were conducted for statistical inference. Correction for multiple statistical comparisons was calculated using Monte-Carlo simulations with AlphaSim (http://afni.nimh.nih.gov/pub/dist/doc/program_help/AlphaSim.html), with an initial cluster-forming single-voxel threshold of $P < 0.001$ (uncorrected), and a grey matter brain mask (Berns *et al.*, 2012), yielding a minimum cluster size of 60 voxels to achieve a whole-brain-corrected cluster-wise threshold of $P < 0.05$. We applied this threshold correction for all group level contrast analyses. AlphaSim is a well-validated method for correction for multiple voxelwise comparisons in neuroimaging studies (Phan *et al.*, 2006; Urry *et al.*, 2006; Bjork and Hommer, 2007).

Correlation analyses

In order to assess relationships between individual's sensitivity to reward or punishment as assessed by the BIS/BAS scales and BOLD responses during reward and avoidance trials, a series of correlation analyses were conducted. We defined functional Regions of interest (ROIs) according to activation clusters identified from each whole-brain contrast of interest. We extracted mean percent signal change values from these activation ROIs for each subject using the Marsbar toolbox (Brett *et al.*, 2002). For the clusters identified within the striatum, signals were separately extracted from the dorsal ($z > 0$ in MNI space) and ventral ($z \leq 0$) parts of the striatum following previous practice (Di Martino *et al.*, 2008; Kätsyri *et al.*, 2013). Pearson correlation coefficient analyses were conducted between extracted ROI values and BIS/BAS scores using the SPSS statistical software package (SPSS Inc., Chicago).

RESULTS

Behavioral results

We examined whether participants learned to choose the target fractals associated with advantageous outcomes by conducting 2 (Valence: Reward *vs* Avoidance) × 2 (Probability: High *vs* Low) ANOVAs on the number of fractal selections and reaction times. A 2 (Valence) × 2 (Probability) ANOVA on the number of selections revealed a significant main effect of Probability, $F(1,18) = 7.77$, $P < 0.05$ (Figure 2a). As expected, participants selected high probability fractals more often (M ± SEM, 34.84 ± 2.26) than low probability fractals (22.50 ± 2.25). The main effect of Valence was not significant, $F < 1.9$, *ns*. No interaction effect was found, $F < 0.1$, *ns*. A 2 (Valence) × 2 (Probability) ANOVA on reaction time revealed a main effect of Valence, $F(1,18) = 7.98$, $P < 0.05$. Reaction times were faster during reward trials (787.04 ms ± 28.26) than avoidance trials (860.95 ms ± 25.91) (Figure 2b). The main effect of Probability was marginally significant, $P < 0.1$. There was a trend for participants responding more quickly for high probability fractals (802.44 ± 24.70) than for low probability fractals (845.55 ± 28.64). No interaction effect was found, $F < 0.1$, *ns*.

We further examined whether participants' target fractal selection improved over time. We calculated the average number of target selection across two blocks with 120 trials each (30 trials per condition per block) as shown in the Table 1. We then performed a 2 (Valence: Reward *vs* Avoidance) × 2 (Time: Block 1 *vs* Block 2) ANOVA on the number of target fractal selections. We found no significant main effects of Valence and Time, $Fs < 1.7$; however, a significant Valence by Time interaction effect was observed, $F(1,18) = 5.08$, $P < 0.05$. Follow-up comparisons indicated that target selections improved from block 1 (16.37 ± 2.05) to block 2 (18.84 ± 2.38) for reward trials, $t = 2.31$, $P < 0.05$; whereas no such change was found over blocks (block 1, 17.53 ± 0.90; block 2, 16.95 ± 0.96) for avoidance trials, $t < 1$. Similarly, we performed a 2 (Valence: Reward *vs* Avoidance) × 2 (Time: block 1 *vs* 2) ANOVA on reaction times. We found a significant main effect of Time, $F(1,18) = 14.37$, $P < 0.001$ and an interaction effect of Valence by Time, $F(1,18) = 5.17$, $P < 0.05$. Follow-up comparisons indicated that reaction times improved from block 1 (842.22 ± 35.54) to block 2 (710.50 ± 36.72) for reward trials, $t = 5.20$, $P < 0.0001$; whereas marginal improvement was found over blocks (block 1, 869.42 ± 27.16; block 2, 808.43 ± 36.85) for avoidance trials, $t = 1.88$, $P = 0.077$.

Next, we examined whether improvement in behavioral measures (number of target selections and reaction times) over blocks were associated with individual differences in reward and punishment sensitivity by conducting Pearson correlation coefficient analyses between behavioral changes over blocks and BIS/BAS scores. We found a marginal trend that people with high BIS scores tended to show less improvement in the number of target selections over blocks for reward trials, $r = -0.45$, $P = 0.061$. No significant correlations were found between BIS/BAS scores and reaction time change over blocks ($P > 0.3$).

FMRI responses during anticipation

Neural regions significantly activated during anticipation are listed in Table 2. Anticipating monetary reward (in comparison to the corresponding neutral condition) elicited activation in the striatum bilaterally and right inferior orbitofrontal gyrus (Figure 3a). In contrast, anticipating loss avoidance (in comparison to its corresponding control condition) elicited a distributed pattern of activations in brain regions including the bilateral striatum, bilateral insula extending to the lateral OFC (BA47), posterior medial frontal gyrus [posterior medial frontal regions (pMFC), BA 8, 32] and posterior part of the cingulate (BA 23) (Figure 3b).

Brain areas commonly involved in both types of reward and avoidance anticipation were identified by a conjunction analysis using an inclusive mask with a threshold level of 0.005 (uncorrected). Regions of common activation were found in the bilateral dorsal caudate and the bilateral anterior insula extending to the lateral OFC (Table 3).

Correlations between BIS/BAS scores and neural activity during anticipation. We found that BAS scores were negatively correlated with activation during loss avoidance anticipation in the pMFC (BA32), $r = -0.535$, $P < 0.05$, and posterior cingulate region (BA23), $r = -0.480$, $P < 0.05$. BIS scores were negatively correlated with activity

Table 1 Average numbers of fractal selections and reaction times as functions of Time (block 1 *vs* block2), Probability (high *vs* low) and Valence (reward *vs* avoidance *vs* neutral R *vs* neutral A)

	Block 1		Block 2	
	High (M ± s.d.)	Low (M ± s.d.)	High (M ± s.d.)	Low (M ± s.d.)
Number of target selections				
Reward	16.37 ± 8.92	12.68 ± 8.83	18.84 ± 10.39	9.84 ± 10.71
Avoidance	17.53 ± 3.92	11.11 ± 3.81	16.95 ± 4.20	11.37 ± 3.76
Neutral R	13.68 ± 6.53	15.11 ± 6.77	12.79 ± 6.80	16.21 ± 6.78
Neutral A	13.26 ± 5.84	15.79 ± 6.06	15.05 ± 6.11	14.11 ± 6.52
Reaction times				
Reward	842.21 ± 141.83	847.94 ± 177.12	710.49 ± 160.08	720.61 ± 165.03
Avoidance	869.41 ± 118.41	908.84 ± 139.72	808.43 ± 160.61	847.27 ± 154.42
Neutral R	891.57 ± 135.92	873.51 ± 90.63	765.44 ± 210.10	768.46 ± 163.18
Neutral A	898.99 ± 118.88	871.61 ± 128.03	753.62 ± 140.60	748.15 ± 175.48

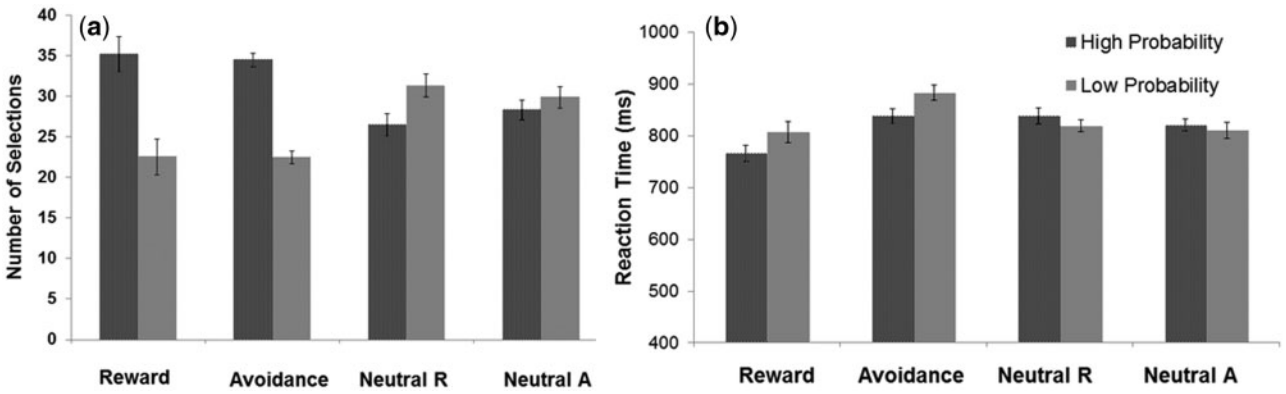

Fig. 2 Illustrations of the average number of fractal selections (**a**) and reaction times (**b**) for each trial type. Error bars indicate the standard errors of the mean.

Table 2 Brain regions activated during the anticipation phase

Anticipation phase	HEM	BA	Coordinates (MNI)			k (volume)	Z
			x	*y*	*z*		
Reward—neutral							
Pallidum	L		−12	8	−4	221	4.55
Caudate	L		−10	4	12	(LM)	4.07
Pallidum	R		16	0	−6	215	4.37
Caudate	R		14	8	8	(LM)	3.83
Putamen	R		18	10	−2	(LM)	3.28
Inf. Orbitofrontal G.	R	47	38	32	−4	165	3.83
Loss avoidance—neutral							
Caudate	R		14	6	12	1631	5.42
Pallidum	L		−10	0	2	(LM)	5.21
Insula	R	47	36	22	−6	1015	4.76
Insula	R	48	42	18	2	(LM)	4.69
Insula	R	48	34	20	8	(LM)	4.61
Insula	L	48	−34	16	−6	362	4.31
Insula	L	48	−32	18	8	(LM)	3.68
Sup. Med. Frontal G.	R	8	4	36	44	821	4.62
SMA	R	8	4	22	56	(LM)	4.42
Mid. Cingulate	R	32	8	36	34	(LM)	3.70
Post. Cingulate	L	23	−6	−24	32	176	4.37
Post. Cingulate	R	23	4	−28	28	(LM)	3.95
Precentral G.	R	6	40	2	50	1076	4.92
Mid. Frontal G.	R	45	44	30	36	(LM)	4.68
Fusiform G.	L	37	−40	−50	−22	284	4.26
Inf. Occipital G.	L	19	−50	−72	−8	(LM)	3.88
Inf. Occipital G.	L	19	−44	−70	−16	(LM)	3.77
Inf. Parietal G.	L	40	−30	−52	42	382	4.18
Inf. Parietal G.	L	40	−40	−46	46	(LM)	3.71
Sup. Parietal G.	L	7	−28	−68	48	(LM)	3.31
Inf. Parietal G.	R	40	40	−56	44	336	4.05
Mid. Occipital G.	R	19	32	−74	34	(LM)	3.81
Sup. Occipital G.	R	7	30	−70	42	(LM)	3.43
Precuneus	R	7	10	−72	46	302	4.97
Precuneus	R	7	8	−72	36	(LM)	4.30
Precuneus	R		8	−60	50	(LM)	3.58
Cerebellum	L		−14	−82	−36	150	4.37
Cerebellum	R		12	−80	−34	56	3.60

Clusters survived a corrected family wise error rate of $P < 0.05$, defined by Monte Carlo simulations using Alphasim. Local maximum for these clusters are denoted with (LM). BA, Brodmann's area; HEM, hemisphere; L, left; R, right; k, volume in voxel units; Z, maximal Z score for contrast; Inf., inferior; Sup., superior; Mid., middle; Med., medial; SMA, supplementary motor area; G., gyrus.

in the left dorsal striatum, $r = -0.493$, $P < 0.05$, during anticipation of loss avoidance (Figure 3) and marginally with activity in the right dorsal striatum, $r = -0.45$, $P = 0.058$.

FMRI responses during feedback reception

Brain regions significantly activated during feedback reception are listed in Table 4. Reception of monetary reward relative to its corresponding control condition elicited increased activation in the caudate bilaterally (Figure 4a). Loss avoidance elicited activation in brain regions, including the right superior frontal gyrus and right middle frontal gyrus (BA10, 11, 47) (Figure 4b). Reception of monetary loss relative to its corresponding control condition elicited increased activation in several brain regions including the bilateral inferior orbitofrontal gyrus (BA 47, ventrolateral PFC), superior medial frontal gyrus (BA 24, 32,9) and left insula (Figure 4c).

We performed conjunction analyses to identify brain regions more selectively associated each type of feedback reception. First, brain regions specifically involved in the rewarded feedback as opposed to unrewarded feedback were characterized as regions showing activation in the contrast of [(rewarded reward trials—unrewarded reward trials)—(scrambled/neutral R trials—unscrambled/neutral R trials)] with an inclusive mask of (rewarded/reward trials–scrambled/neutral

Table 3 Conjunction of reward anticipation and avoidance anticipation using an inclusive mask at the threshold of $P < 0.005$, uncorrected

	HEM	BA	Coordinates (MNI)			k (volume)	Z
			x	*y*	*z*		
Caudate	R		14	6	12	311	5.42
Caudate	L		−14	4	14	246	5.06
Insula/Inf. Orbitofrontal G	R	47	34	22	−6	385	4.72
			44	18	−6	(LM)	3.93
Insula	L	47	−32	20	−4	74	4.31

Clusters survived a corrected family wise error rate of $P < 0.05$, defined by Monte Carlo simulations using Alphasim ($P < 0.001$ uncorrected, k = 60). Local maximum for these clusters are denoted with (LM). BA, Brodmann's area; HEM, hemisphere; L, left; R, right; k, volume in voxel units; Z, maximal Z score for contrast; Inf., inferior; G., gyrus.

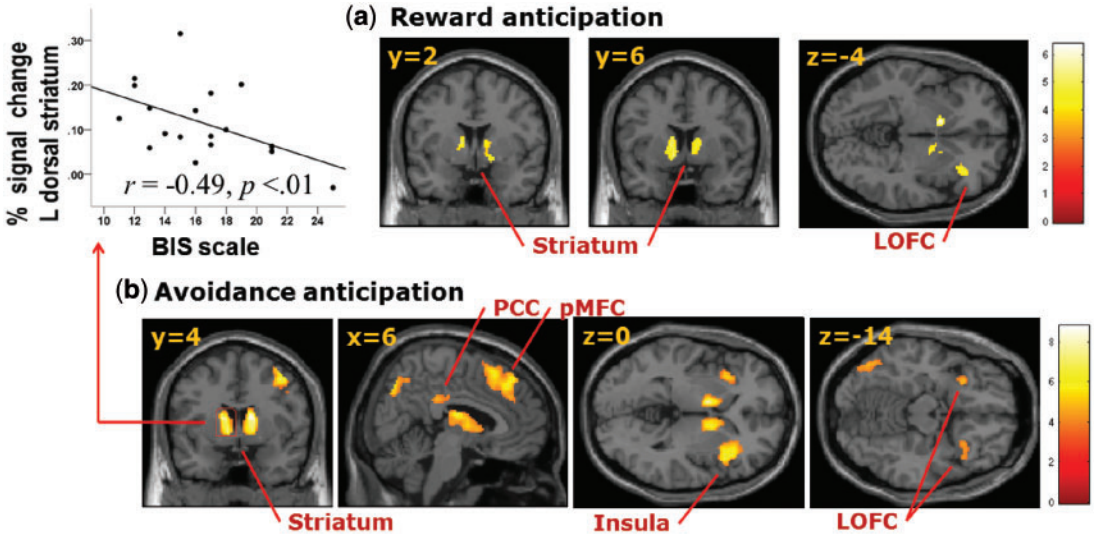

Fig. 3 Neural regions activated during anticipation of monetary reward (**a**) and loss avoidance (**b**). The scatter plot illustrates correlation between the BIS scale and signals from the left dorsal striatum during anticipation of loss avoidance.

Table 4 Brain regions activated during the reception phase

Reception phase	HEM	BA	Coordinates (MNI)			k (volume)	Z
			x	*y*	*z*		
Rewarded—neutral							
Caudate	R		10	6	2	385	4.63
Caudate	R		12	8	−10	(LM)	3.95
Caudate	R		12	4	16	(LM)	3.89
Pallidum	L		−8	4	2	299	4.45
Caudate	L		−10	4	14	(LM)	4.32
Caudate	L		−12	−4	18	(LM)	3.49
Unrewarded—neutral							
No activation							
Unpunished (loss avoidance)—neutral							
Mid. Frontal G.	R	47	36	50	0	60	4.53
Mid. Frontal G.	R	11	28	54	0	(LM)	3.40
Sup. Frontal G.	R	8	30	26	54	304	4.11
Mid. Frontal G.	R	8	30	16	58	(LM)	4.04
Mid. Frontal G.	R	9	36	28	48	(LM)	3.71
Precuneus	R	7	4	−62	50	74	4.09
Precuneus	L	7	−4	−62	52	(LM)	3.72
Cerebellum	L		−12	−78	−24	316	4.17
Cerebellum	L		−16	−82	−34	(LM)	3.95
Cerebellum	L		−6	−82	−30	(LM)	3.86
Punished—neutral							
Inf. Orbitofrontal G.	R	38	48	20	−10	229	4.33
Inf. Orbitofrontal G.	R	47	42	30	−8	(LM)	3.71
Inf. Orbitofrontal G.	R	47	36	22	−8	(LM)	3.51
Insula	L	48	−28	14	−16	180	4.17
Inf. Orbitofrontal G.	L	47	−34	30	−20	(LM)	4.05
Int. Orbitofrontal G.	L	38	−42	24	−16	(LM)	3.99
SMA	R	8	8	24	64	910	5.23
Sup. Med. Frontal G.	L	9	−2	48	46	(LM)	4.31
Sup. Med. Frontal G.	L	9	2	38	40	(LM)	3.97
Cerebellum	L		−42	−68	−28	446	4.53
Cerebellum	L		−18	−84	−30	(LM)	3.94
Cerebellum	L		−32	−80	−20	(LM)	3.70

Clusters survived a corrected family wise error rate of $P < 0.05$, defined by Monte Carlo simulations using Alphasim ($P < 0.001$ uncorrected, k = 60). Local maximum for these clusters are denoted with (LM). BA, Brodmann's area; HEM, hemisphere; L, left; R, right; k, volume in voxel units; Z, maximal Z score for contrast; Inf., inferior; Sup., superior; Mid., Middle; Med., medial; G., gyrus.

R trials) at the threshold level of $P < 0.005$, uncorrected. This conjunction analysis yielded activation in the bilateral caudate (Table 5). Similarly, brain regions more involved in loss avoidance than loss were characterized as the regions that showed greater activation in the contrast of [(unpunished/avoidance trials—punished/avoidance trials)—(no feedback/neutral A trials—scramble feedback/neutral A trials)] with an inclusive mask of (unpunished/avoidance trials—no feedback/neutral A trials) contrast. This analysis identified activated regions in the right superior and middle frontal cortex (Table 5). Finally, brain regions more specifically involved in loss reception than loss avoidance were characterized as the regions that showed greater activation in the contrast of (punished/avoidance trials—unpunished/avoidance trials)—(scrambled /neutral A trials—unscrambled/neutral

Table 5 Conjunction of responses during reception phase using an inclusive mask at the threshold of $P < 0.005$, uncorrected

Reception phase	HEM	BA	Coordinates (MNI)			k (volume)	Z
			x	*y*	*z*		
(Rewarded—unrewarded) masked with (rewarded—neutral)							
Caudate	L		−10	6	4	140	4.49
Caudate	L		−10	0	14	(LM)	3.67
Caudate	R		10	8	2	106	4.21
Caudate	R	25	10	6	−10	(LM)	3.70
(Unpunished—punished) masked with (unpunished—neutral)							
Mid. Frontal G.	R	9	32	30	50	61	3.68
Sup. Frontal G.	R	8	28	18	58	(LM)	3.66
(Punished—unpunished) masked with (punished—neutral)							
Sup. Medial Frontal G.	R	10	4	56	26	326	4.63
Sup. Medial Frontal G.	L	10	−4	50	30	(LM)	4.51
Sup. Frontal G.	L	10	14	54	34	(LM)	3.84
Ant. Cingulate G.	R	24	2	30	26	134	4.08

Clusters survived a corrected family wise error rate of $P < 0.05$, defined by Monte Carlo simulations using Alphasim ($P < 0.001$ uncorrected, k = 60). Local maximum for these clusters are denoted with (LM). BA, Brodmann's area; HEM, hemisphere; L, left; R, right; k, volume in voxel units; Z, maximal Z score for contrast; Inf., inferior; Sup., superior; Mid., Middle; Med., medial; G., gyrus.

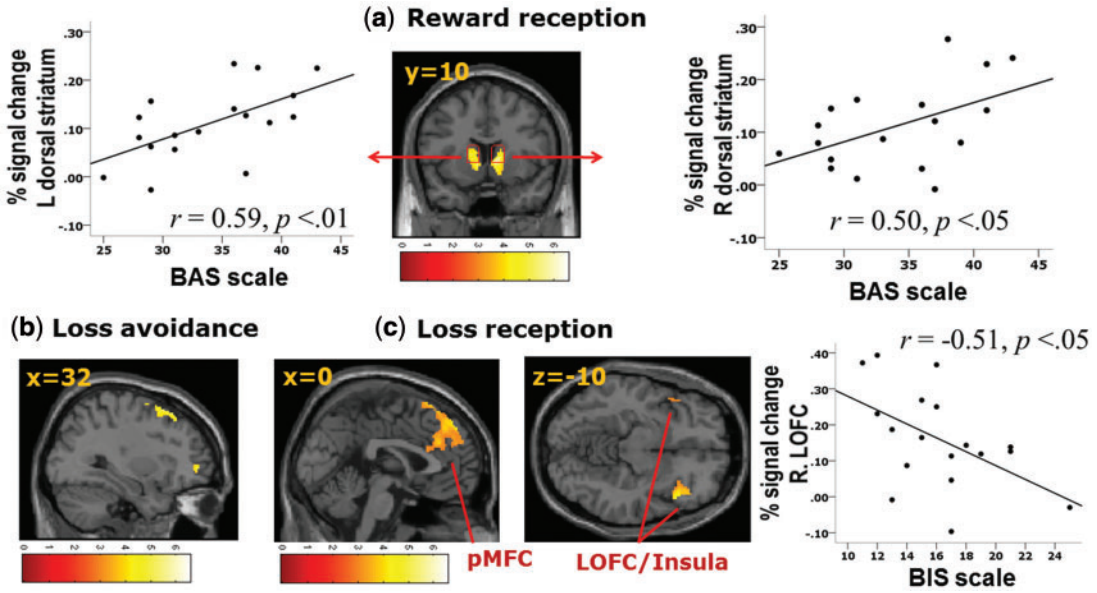

Fig. 4 Neural regions activated during reception of reward (**a**), loss avoidance (**b**), and monetary loss (**c**). Scatter plots placed in the upper low illustrate correlation between the BAS scale and signals change from the left and right ventral striatum during reward reception. The scatter plot placed in the bottom row illustrates correlation between the BIS scale and signal change from the right inferior orbitofrontal cluster during loss reception.

A trials)] with an inclusive mask of (punished/avoidance trials—scrambled/neutral A trials) contrast. This analysis yielded activations in medial frontal cortex (BA10) and anterior cingulate (BA24).

Correlations between BIS/BAS scale and neural activity during feedback reception. Correlation analyses revealed that greater trait sensitivity to reward assessed by the BAS tended to be positively correlated with BOLD responses in the left and right ventral striatum during reward reception, $r = 0.591$, $P < 0.01$ and $r = 0.497$, $P < 0.05$, respectively (Figure 4). On the other hand, greater sensitivity to punishment was negatively correlated with neural activity in the right inferior orbitofrontal cluster during the reception of monetary loss, $r = -0.512$, $P < 0.05$ (Figure 4). No other significant correlations were found.

DISCUSSION

In this study, we investigated the neural correlates of reward and avoidance learning and examined how these correlates are modulated by individual differences in sensitivity to reward and punishment. Behaviorally, participants overall learned to choose fractals associated with higher (*vs* lower) probabilities of advantageous outcomes more often to a similar extent for both reward and avoidance trials; however, they showed specific time-related improvement across blocks in target selection and response speed for reward trials but not for avoidance trials. Differential brain responses were also observed across reward and avoidance trials. We found that the ventral striatum was specifically activated during reward anticipation, whereas the dorsal striatum was commonly activated during both reward and avoidance anticipation as revealed by conjunction analysis. During avoidance anticipation, additional activations were observed in the bilateral anterior insula, right lateral OFC, pMFC and posterior cingulate region. During reward reception, the striatum (extending to the ventral and dorsal sectors) was activated bilaterally. Successful loss avoidance, on the other hand, activated right-lateralized prefrontal regions including the ventrolateral (BA47) and dorsolateral PFC (BA 8, 9). Receiving monetary loss activated the lateral OFC (BA47) and pMFC (BA8, 9). Consistent with our predictions, we found that individuals' sensitivity to reward (as assessed by BAS) was positively associated with increased activation in the left and right ventral striatum while receiving reward. On the other hand, sensitivity to punishment (as assessed by BIS) was negatively associated with activation in the left dorsal striatum during avoidance anticipation and also with activation in the right lateral OFC during receiving monetary loss. These results are broadly consistent with previous findings of the role of the striatum in reward learning and also suggest distinctive contributions of the reward and punishment sensitivity in neural substrates of learning to gain reward and to avoid punishment (Gray, 1987; Knutson and Cooper, 2005).

Neural correlates of anticipating outcomes

Conjunction analyses between reward anticipation and avoidance anticipation identified common activations in the bilateral dorsal caudate. On the other hand, as seen in the Table 2, the ventral striatum was activated only during reward anticipation but not during loss avoidance anticipation. This finding, together with behavioral improvement over time seen only during reward trials, is consistent with previous suggestions that the ventral striatum is more specifically involved in learning the value of pleasant reward associated with a particular stimulus, whereas the dorsal striatum is more specifically involved in forming habitual action selection during reward learning (O'Doherty *et al.*, 2004; Tricomi *et al.*, 2009; Palminteri *et al.*, 2012). The lack of ventral striatal activation during anticipation in the avoidance trials might be associated with the absence of explicit reward and rather intrinsic nature of the advantageous outcomes (such as loss avoidance) during avoidance learning. The bilateral anterior insula extending to the lateral OFC was also activated commonly for both types of anticipation, as identified by conjunction analyses. The anterior insula constitutes a part of the somatic marker network (Damasio, 1995) and has been implicated in the interoception of physiological states elicited during emotional experience (Damasio *et al.*, 2000; Blood and Zatorre, 2001; Cunningham *et al.*, 2004; Naqvi and Bechara, 2010; Palminteri *et al.*, 2012). Activation of the anterior insula suggests that the interoceptive representations of monetary outcomes associated with fractal selections were retrieved during the anticipatory delays. The lateral OFC was implicated in the evaluation of negative outcomes and also in change of previously learned action (Kringelbach, 2005). Activation of this region during anticipation of outcomes may reflect the fact that each selection of a fractal stimulus could result in negative consequences such as lack of monetary reward or monetary loss even if the participants chose the high probability fractal.

In addition to the striatum and insula/lateral OFC, additional activations were observed during avoidance anticipation in regions including the pMFC, posterior cingulate and posterior parietal cortex (PPC). The pMFC has been suggested to play a critical role in monitoring negative or unfavorable consequences (Ridderinkhof *et al.*, 2004). The posterior cingulate cortex is structurally well connected with the medial prefrontal regions and striatum (Vogt *et al.*, 1992), and its activity has been associated with internally focused attention (Raichle *et al.*, 2001; Buckner *et al.*, 2008). The intrinsic nature of reinforcers in avoidance learning (Kim *et al.*, 2006) might direct attention more internally. That is, during avoidance learning, action is rewarded not by external reward but by the absence of loss. Therefore in order to meaningfully evaluate the rewarding property of loss avoidance, the internal representation of loss would still need to be activated. The PPC has been implicated in the representation of salience (unsigned magnitude) of predictive cues that influences the decision process (Kahnt and Tobler, 2013; Kahnt *et al.*, 2014). Given that both reward and avoidance trials had same level of salience (i.e. winning or losing 1000 KRW), it is somewhat unexpected that PPC activation was only observed during avoidance trials. Alternatively, posterior parietal regions have also been implicated in directing attention to internally generated mnemonic representations (Wagner *et al.*, 2005; Cabeza *et al.*, 2008). Therefore, activation in the PPC during avoidance anticipation may indicate increased attentional orientation to internal representations associated with selected fractals.

It is notable that the striatal contribution to the representation of reward value was shown to be dependent on whether the relevant experimental task required the execution of an action (Guitart-Masip *et al.*, 2012, 2014). For example, when action was required in learning reward values of predictive cues, striatal activity was positively associated with the learned value; however, when no action was required, the relationship between striatal activity and learned value was negative (Guitart-Masip *et al.*, 2012). Given that all trials in the current study required action, activation of the dorsal striatum observed during reward and avoidance anticipation might be associated with the representation of valence-free action value whereas activation of the ventral striatum that was observed only during reward anticipation might be associated with representation of valence-specific action value.

Neural correlates of feedback reception

We found increased activation in the bilateral caudate (extending to both the ventral and dorsal regions) when participants received monetary reward. This finding is in line with the view that the striatum is specifically involved in the representation of positive subjective value of a stimulus (McClure *et al.*, 2004; Knutson and Cooper, 2005). Striatal activation was not observed during the avoidance of monetary loss, even though avoidance of monetary loss was as equally

advantageous as obtaining monetary gain for successful task performance. Avoidance of monetary loss instead activated right-lateralized prefrontal regions (BA 8, 9; Tables 4 and 5). The lateral prefrontal cortex has been associated with attentional control during reward learning (Hampshire *et al.*, 2012). These findings may point to a greater role of attentional and cognitive control in loss avoidance compared with reward gain. That is, the appropriate appraisal of loss avoidance as a meaningful outcome during avoidance trials appears to require one's attention to the learning context and their awareness of potential loss outcomes. Activation of the right lateral prefrontal region during the loss avoidance feedback as compared with striatal activation during reward reception suggests that one's subjective experience of avoiding loss is qualitatively different from that of receiving explicit reward.

Receiving monetary loss activated the lateral OFC (BA47) and pMFC (BA 8, 9). This finding is consistent with previous results associating the lateral OFC with the representation of loss or punishment feedback (O'Doherty *et al.*, 2001; Gottfried *et al.*, 2002) and the medial PFC with monitoring of unfavorable outcomes (Ridderinkhof *et al.*, 2004). In general, the pattern of neural activations observed during the reception period is in line with previous neuroimaging studies of reinforcement learning but our results further suggest that the neural representation of outcome values of reward and loss avoidance are separable despite their comparable task performance.

Correlation with BIS/BAS scores

Greater sensitivity to reward as assessed by the BAS scale was found to be associated with increased activation in the ventral striatum bilaterally during reward reception. This result is consistent with a previous neuroimaging study showing that individuals with greater reward sensitivity have elevated reactivity in the ventral striatum when they received a monetary reward (Simon *et al.*, 2010). Given that the ventral striatum is thought to represent the positive subjective value of a stimulus (McClure *et al.*, 2004; Knutson and Cooper, 2005), these correlational results may suggest that individuals with greater reward sensitivity may experience greater subjective positive emotion with a rewarding stimulus as compared with individuals with lower reward sensitivity. This view is in line with a recent structural brain imaging study showing that, across individuals, reduced volume in the anterior caudate and ventral striatum was associated with reduced ability to experience hedonic feelings in everyday life, as assessed by trait anhedonia (Harvey *et al.*, 2007). Sensitivity to reward in this study was not correlated with neural activity during reward anticipation, but showed negative correlation with activity in the pMFC and posterior cingulate during avoidance anticipation. This result suggests that people with greater BAS may have reduced sensitivity in monitoring loss and increased externally focused attention during avoidance learning. This interpretation is consistent with recent findings from clinical neuroimaging studies showing increased ventral striatal activity during a monetary reward task in atypical adolescents and adults with extreme BAS levels as those found in externalizing disorders including oppositional defiant disorder and conduct disorder (Bjork *et al.*, 2010), and psychopathy (Hundt *et al.*, 2008; Buckholtz *et al.*, 2010).

Sensitivity to punishment was negatively associated with activation in the left dorsal striatum during avoidance anticipation. Given that the dorsal striatum is implicated in forming stimulus and action associations (O'Doherty, 2004; Tricomi *et al.*, 2009), this result may explain typical behaviors under the influence of the BIS: passive avoidance and giving up actions in the absence of immediate reward (Gray, 1987). Alternatively, the observation that participants with reduced punishment sensitivity had a greater activation in the dorsal striatum suggests that they might have a tendency to experience a pleasurable 'thrill' of avoiding loss as compared with participants with greater punishment sensitivity.

While receiving monetary loss, participants with greater BIS scores showed reduced activity in the lateral OFC. Given that people with greater BIS are more sensitive to punishment or negative consequences (Gray, 1987) and that the lateral OFC is implicated in the representation of punishment/loss during reinforcement learning (O'Doherty *et al.*, 2001; Gottfried *et al.*, 2002; Elliott *et al.*, 2010), this result is rather unexpected. We speculate that monetary loss feedback may have been perceived to be of relatively little personal significance and, therefore, was less likely to recruit regulatory processes, processes which otherwise might have been more pronounced in people with greater BIS scores.

CONCLUSION

In this study, we identified different sets of brain regions involved in learning to gain monetary reward and learning to avoid monetary loss. Learning to gain reward was primarily dependent on striatal resources across both anticipation and reception periods. In contrast, learning to avoid loss was associated with activation of different sets of brain regions between the anticipation and reception phases. Furthermore, learning to avoid loss recruited the dorsal striatum as well as prefrontal regions including the pMFC and lateral PFC. The recruitment of additional prefrontal resources involved in avoidance learning may reflect the more complex and demanding nature of cognitive mechanisms required for avoidance learning. For the proper evaluation of outcome value during avoidance learning, the activation of the representation of the learning context appears to play an important role. Individual differences in reward and punishment sensitivity were found to be associated with differential neural activation during anticipation and reception periods of reward and avoidance learning. Our results suggest that individuals with greater reward sensitivity are more reactive to rewarding outcomes but are less sensitive to monitoring loss. On the other hand, individuals with greater punishment sensitivity utilized fewer resources in the dorsal striatum in forming an association between action and loss avoidance. In this study, we provide evidence that trait sensitivity to reward and punishment play distinctive modulatory roles in brain regions sensitive to the anticipation and reception of reward and loss avoidance. These findings add to the current understanding of neural basis of reinforcement learning and can contribute to the elucidation of neural mechanisms underlying psychopathological problems associated with extreme sensitivity to reward and punishment.

Conflict of Interest

None declared.

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