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Reward Sensitivity Modulates Connectivity Among Reward Brain Areas When Processing Anticipatory Reward Cues

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Abstract

Reward sensitivity or the tendency to engage in motivated approach behavior in the presence of rewarding stimuli, may be a contributing factor to vulnerability to disinhibitory behaviors. While evidence exists for a reward sensitivity-related increased response in reward brain areas (i.e., nucleus accumbens or midbrain) during the processing of reward cues, it is unknown how this trait modulates brain connectivity, specifically the crucial coupling between the nucleus accumbens, the midbrain, and other reward-related brain areas including the medial orbitofrontal cortex and the amygdala. Here, we analyzed the relationship between effective connectivity and personality in response to anticipatory reward cues. Forty-four males performed an adaptation of the Monetary Incentive Delay Task and completed the Sensitivity to Reward scale. The results showed the modulation of reward sensitivity on both activity and functional connectivity (psychophysiological interaction) during the processing of incentive cues. Sensitivity to reward scores related to stronger activation in the nucleus accumbens and midbrain during the processing of reward cues. Psychophysiological interaction analyses revealed that midbrain-medial orbitofrontal cortex connectivity was negatively correlated with sensitivity to reward scores for high compared with low incentive cues. Also, nucleus accumbens-amygdala connectivity correlated negatively with sensitivity to reward scores during reward anticipation. Our results suggest that high reward sensitivity-related activation in reward brain areas may result from associated modulatory effects of other brain regions within the reward circuitry.

Introduction

Reward sensitivity is a trait that predisposes to a variety of disinhibited disorders, including attention deficit hyperactivity disorder, psychopathy, drug abuse and addiction, pathological gambling, and eating disorders (see Bijttebier et al., 2009 for review). Behavioral studies have associated this trait with enhanced reward processing and learning, preference for immediate reward and lower inhibitory control in reward contexts (Ávila & Torrubia, 2008; Corr, 2004), as well as active avoidance under punishment contingencies (Gray 1981, 1991; Smillie and Jackson, 2005).

The brain regions of the dopaminergic reward system are thought to be the neural substrate for individual differences in reward sensitivity (Depue & Collins, 1999; Gray, 1991; Pickering and Gray, 2001). The neural structure of the dopaminergic reward system forms a loop in which dopaminergic midbrain areas, such as the ventral tegmental area (VTA) and substantia nigra (SN) complex, send projections to limbic and prefrontal brain areas, and receive afferent fibers from most of these areas (Düzel et al., 2009; Haber & Knutson, 2010). A broad literature links this system to motivation and goal-directed behaviors, and the system is thought to modulate diverse cognitive processes that allow the attainment of reward and the relief from punishment (see Berridge, 1998 for review).

Individual differences in reward sensitivity have been associated with the structural and functional variability of definite reward-related areas within the dopaminergic system. For example, individuals with high reward sensitivity show diminished striatum volume (Barrós-Loscertales et al., 2006), increased white-matter tract strength between the nucleus accumbens (NAcc) and amygdala (Cohen et al., 2009), more random resting-state neural dynamics (or irregular fluctuating time series) in the NAcc and orbitofrontal cortex (Hahn et al., 2012), and increased NAcc and

midbrain response to reward anticipation (Beaver et al., 2006; Cámara et al., 2010; Carter et al., 2009; Hahn et al., 2009). Although these studies provide evidence that reward sensitivity modulates the structure and functioning of brain reward areas, the role of this trait in the connectivity between these regions remains unclear.

In this paper, we studied how individual differences in reward sensitivity modulate the activity and functional connectivity of reward brain areas during processing of valence and incentive magnitude in a monetary incentive delay (MID) task. This paradigm involves approach and active avoidance processes supposedly mediated by individual differences in reward sensitivity according to Gray's model (Avila, 2001; Smillie and Jackson, 2005; Arnett and Newman, 2000). Previous functional magnetic resonance imaging (fMRI) studies have been focused on the relation between reward sensitivity and reward cues involving the NAcc, midbrain, orbitofrontal cortex, and amygdala (Beaver et al., 2006; Carter et al., 2009; Hahn et al., 2009). However, no previous fMRI studies have considered the involvement of reward sensitivity in brain reactivity to both approach and active avoidance cues as others have investigated behaviorally (Arnett & Newman, 2000; Smillie & Jackson, 2005). Based on previous reports, we hypothesized an enhanced response of brain reward areas (e.g., NAcc, orbitofrontal cortex) during the processing of the motivational valence of cues by individuals with stronger reward sensitivity. Moreover, we explored the relation between reward sensitivity and brain areas involved in processing incentive magnitude of stimuli independently of their valence. Finally, we studied the regional brain connectivity among reward-related areas associated with individual differences in reward sensitivity.

Methods

Participants

Forty-four male undergraduates (age = 23.4 ± 4.1 ; years of education = 13.8 ± 2.2) participated in this fMRI study. Participants were physically and psychologically healthy with no history of mental disorders, head trauma, or drug abuse. All participants signed written informed consent prior to participation. The study was approved by the ethical committee of the University Jaume I. All study procedures conform with The Code of Ethics of the World Medical Association (Declaration of Helsinki; printed in the British Medical Journal 18 July 1964).

Measure of Reward Sensitivity

All participants completed the Sensitivity to Punishment and Sensitivity to Reward Questionnaire (Torrubia et al., 2001) as a measure of reward sensitivity. The mean Sensitivity to Reward (SR) score was 11.72 (SD = 4.65, range: 2–24), and scores followed a normal distribution (Kolmogorov-Smirnov test: $D = .113$, $p > .10$). Thus, these scores were consistent with those obtained from other samples (Barros-Loscertales et al., 2006, 2010; Torrubia et al., 2001). The Sensitivity to Punishment and Sensitivity to Reward Questionnaire has been translated into 15 languages and is widely used to assess reward sensitivity in adults (Torrubia et al., 2008) and children (Luman et al., 2012). Previous studies have shown that the SR scale has good content validity and strongly correlates with other measures of reward sensitivity such as reward responsiveness, drive, fun seeking, novelty seeking, and impulsivity scales (see Torrubia et al., 2008 for review).

Experimental Design and Stimuli

The goal of our experiment was to analyze the association between individual differences in reward sensitivity, and the functional activity and effective connectivity

of reward brain areas during the anticipation of monetary incentives. We used an adaptation of the MID task described by Knutson et al. (2001, 2003) including all high and low reward and punishment conditions (see supplementary material, **Figure S1**). Before entering the scanner, all participants were given instructions on the task and completed a practice session. The practice session was thought to minimize later learning effects and provided an estimate of each individual's reaction time (RT) to standardize task difficulty within the scanner. For each participant, the median RT of correct trials during the practice session was implemented as a cut-off RT in the main experiment. All participants were initially paid 20 euros for their participation. At the end of the experiment, participants received an individually adjusted bonus depending on their performance in the experimental task.

Inside the scanner, participants performed two 8-minute runs of the MID task. Each run consisted of 60 trials for a total of 120 trials. There were four kinds of events defined by a high reward, low reward, high punishment, and low punishment cue. Each trial consisted of one of those cues presented for 500 ms, followed by a black screen of variable duration (2,000–2,250 ms) and then by a white target square that appeared for 100 ms to which participants had to respond by pressing a response button as quickly as possible. After the participant responded, a black screen with a variable duration of 2,000–4,000 ms appeared, followed by a feedback screen (1,500 ms duration) that notified participants of whether they had won or lost money during that trial and indicated their cumulative total at that point. As previously noted, each event was defined by the initial appearance of a different cue: a circle with two horizontal lines, indicating the possibility of winning 3 euros (high reward cue; $n = 24$); a circle with one horizontal line, indicating the possibility of winning 0.20 euros (low reward cue; $n = 24$); a square with two horizontal lines, indicating the chance to avoid losing 3 euros

(high punishment cue; $n = 24$); and a square with one horizontal line, indicating the chance to avoid losing 0.20 euros (low punishment cue; $n = 24$). Therefore, the cues informed participants of the potential valence of the outcome (reward, punishment) and its incentive magnitude (high, low). A triangle ($n = 24$) was the cue for non-incentive trials in which participants neither won nor lost money. Participants had to respond after each incentive cue, but they did not respond to non-incentive cues because these cues were not followed by a target stimulus (white square). We modified the original MID task in this way in order to perform comparisons without disentangling reward anticipation from action preparation. These comparisons may produce interesting results when analyzing the effects of modulation of brain processing by reward sensitivity since the effects of individual differences on instrumental approach and active avoidance behavior may arise from the joint effects of valence (Hahn et al., 2009) and motor responses in our regions of interest (ROIs; e.g., striatum; see Guitart-Masip et al., 2011). On the other hand, it is likely responsible for the dependent variable of interest in all previous behavioral studies on reward sensitivity (see Pickering & Gray, 2001 and Avila & Torrubia, 2008 for review). Additionally, we can isolate the motivational effects in our study by means of a factorial design with two valence conditions (reward, punishment) and two incentive magnitude conditions (high, low) since motor effects are controlled for by the motivational conditions.

Trial types were pseudo-randomly ordered within each run. The intertrial interval was randomized between 2,000 ms and 4,000 ms. Participants were instructed to respond as quickly as possible to target stimuli to achieve the rewards or avoid the punishments. The task was programmed and presented using Presentation software (Neurobehavioral Systems, Inc., Albany, CA). Visual stimuli were displayed in the scanner using Visuastim goggles (Resonance Technology, Inc., Northridge, CA).

Stimulus presentation was synchronized with the scanner acquisition using a SyncBox (Nordic NeuroLab, Bergen, Norway) and behavioral task performance was recorded with a ResponseGrip (Nordic NeuroLab, Bergen, Norway).

FMRI Acquisition

Image acquisition was performed using a 1.5T Siemens Avanto MRI scanner (Siemens, Erlangen, Germany). Functional images were acquired using a T2*-weighted echo-planar imaging sequence (TR/TE = 2000/30 ms, matrix = 64 x 64 x 30, voxel size = 3.5 mm³, flip angle = 90°, number of volumes per run = 251). Thirty 3.5-mm-thick slices centered parallel to the hippocampi were axially acquired with a 0.5-mm interslice gap. Structural images were acquired using a T1-weighted sequence (TR/TE = 11/4.9 ms, flip angle = 90°, voxel size = 1 mm³), which facilitated the localization and coregistration of functional data.

FMRI Preprocessing and Analysis

The analyses focused on changes in the blood oxygen level-dependent contrast during the anticipatory cue periods. Data were preprocessed and analyzed using the Statistical Parametric Mapping (SPM) 5 software package (Wellcome Trust Centre for Neuroimaging; <http://www.fil.ion.ucl.ac.uk/spm>). The first two scans for each participant in each run were excluded from the analyses to discount any artifacts related to the transient phase of magnetization. For preprocessing purposes, the time series of voxels were interpolated intravolume to a middle slice (in terms of acquisition time) to correct the acquisition of nonsimultaneous slices (slice order: ascending interleaved). Later, motion correction was carried out by taking the first image of the first session as the reference image, obtaining a subsequent realignment average image, and using this average image as a reference for the other session's motion correction. This correction was made using a six-parameter rigid body transformation. An anatomical image for

each participant was coregistered to his average functional image using a rigid body transformation. Then, the anatomical acquisition was segmented and normalized. This normalization was completed according to the Montreal Neurological Institute's (MNI) template by applying an affine transformation followed by nonlinear deformation using the basis functions defined in the SPM program (Ashburner & Friston, 1999). Computed transformation parameters from the anatomical image normalization after segmentation were applied to each participant's functional time series (voxels rescaled to a final voxel size of 3 mm³). Finally, the images were spatially smoothed with a 6-mm isotropic Gaussian kernel.

Significant hemodynamic changes among the conditions were examined using the general linear model (Friston et al., 1995). At the first-level (within-subjects) analysis, a statistical model was computed for each participant by applying a canonical hemodynamic response function combined with its time derivative. The fMRI time series data were high-pass filtered to eliminate low-frequency components. The four conditions of interest (high reward cue, low reward cue, high punishment cue, and low punishment cue) were modeled as separate regressors in a general linear model. Furthermore, we modeled separate regressors for the eight outcomes (win or loss in each incentive trial) and the non-incentive cue. The six motion correction parameters from each participant were included in the model as "nuisance" variables. Finally, statistical contrast images were generated to obtain the brain activation for anticipatory periods.

ROIs

Predefined ROIs included the NAcc, amygdala, medial orbitofrontal cortex (mOFC), and midbrain based on previous studies of reward sensitivity (Beaver et al., 2006; Hahn et al., 2009). All these structures were defined using the AAL (Tzourio-

Mazoyer et al., 2002) or the Wake Forest University PickAtlas (Maldjian et al., 2003) for self-defined ROIs. Discrete ROIs were defined for the amygdala and the mOFC, the latter including the bilateral rectus gyri from the AAL toolbox (Tzourio-Mazoyer et al., 2002). The NAcc was defined as a 6-mm-radius sphere at $\pm 10, 8, -4$ (x, y, z; MNI coordinates based on Cools et al., 2002; Barrós-Loscertales et al., 2006), whereas the midbrain was defined as a 6-mm-radius sphere at $0, -20, -12$ (x, y, z; MNI coordinates based on Telzer et al., 2010), which mainly includes the VTA/SN complex.

FMRI Analysis: Overall Task Activations

FMRI analyses were conducted to study brain areas responding to both the reward and incentive magnitude conditions depending on reward sensitivity. Theoretical models of personality have proposed that reward sensitivity modulates both signals of reward and of relief from punishment (Gray, 1991; Pickering & Gray, 2001). In addition, previous studies have showed that some dopaminergic brain areas respond to the salience of stimuli independent of their valence (Jensen et al., 2007; Knutson et al., 2005). Thus, it is possible that reward sensitivity modulates brain areas responding to both reward and incentive magnitude. To study brain activity related to reward cues and high incentive cues, we performed a two-way (Valence [reward, punishment] x Incentive Magnitude [high, low]) repeated-measures analysis of variance (ANOVA), in a second-level random-effects analysis using the contrast images (high reward, low reward, high punishment, and low punishment) extracted from the first-level analysis.#

Moreover, we implemented a conventional subtraction analysis between the reward cues (high and low) and non-incentive cue (neutral triangle). The objective of this contrast was to study the whole process of reward anticipation, including motivation and motor preparation components given their interest in the analysis of individual differences in personality based on previous comments (see Experimental

Design and Stimuli). We hypothesized that this comparison may change the effect of individual differences on brain activity during reward anticipation, allowing the study of modulation of the ROIs by reward sensitivity. We performed a comparison of reward cues and the non-incentive cue for each participant at the first-level analysis and used the resulting contrast images in a one-sample t test at the second-level analysis. Reported results were those that survived a small volume correction (SVC) with a statistical significance threshold of $p < .05$ (family-wise error [FWE] corrected).#

Analysis of Effects of Rewards Sensitivity on Task-Related Activations#

To analyze the modulatory effect of personality on brain activation, three multiple regression analyses were performed between SR scores and the resulting contrast images obtained in the first-level analysis: 1) reward versus punishment, 2) high incentive versus low incentive, and 3) reward versus neutral. The nuisance effects of age were regressed out. Analyses were carried out on each ROI using SVC with a statistical significance threshold of $p < .05$ (FWE corrected).#

Functional Connectivity Analysis: Psychophysiological Interaction (PPI)#

Following previous studies on personality (Cremers et al., 2010; Haas et al., 2006), connectivity analyses were performed to study the relation between reward brain networks and reward sensitivity. Once we identified the ROIs that showed effects of reward sensitivity on task-related activations, we performed PPI analyses (Friston et al., 1997) using these ROIs as source (seeds) regions to study if connectivity among these areas and the other ROIs was also related to reward sensitivity. These connectivity analyses were performed for the same contrasts of interest (psychological variables; reward vs. punishment, high incentive vs. low incentive, and reward vs. neutral) used to study task-related activations associated with SR scores. This resulted in a total of six independent PPI analyses: 2 regions (right NAcc and midbrain; see Results) x 3

psychological variables (each contrast of interest). For each participant, we extracted the time series from the first eigenvariate of all active voxels within the right NAcc and midbrain ROIs (seed regions). Afterward, the time series were deconvolved, and each PPI was calculated as the element-by-element product of the deconvolved time series and a vector representing the psychological variable (Gitelman et al., 2003). These products were subsequently reconvolved with the hemodynamic response function and entered as regressors in a first-level analysis together with the physiological variable (the time series extracted from the seed region) and the vector of the psychological variable.#

Then, we performed second-level analyses including the PPI regression coefficients (changes in connectivity) in: 1) a one-sample *t* test to assess positive or negative changes in connectivity at group level in each described PPI; and 2) multiple regression analyses using SR scores as a regressor of interest and age as a covariate to investigate the relationship between each measure of connectivity change and SR scores. Once again, the analyses were restricted to the ROI (SVC, $p < .05$, FWE corrected).#

Behavioral Data Analyses#

The percentage of hits (successful responses) and mean of RTs were recorded for each participant. The hits and RTs for each incentive condition were used to perform two different 2 x 2 (Valence [reward, punishment] x Incentive Magnitude [high, low]) repeated-measures within-subjects ANOVAs to study cue-related effects on behavioral performance. To investigate personality effects, we used correlations and partial correlations with performance variables (hits and RTs).#

Results

Behavioral Results#

Mean RTs and percentage of hits appear in **Figure 1** and **Table 1**. The repeated-measures ANOVA for RTs yielded main effects of valence, $F(1, 43) = 5.69, p = .022$, and incentive magnitude, $F(1, 43) = 5.87, p = .02$, indicating faster RTs for reward than for punishment conditions, and for high than for low incentive conditions. These main effects were qualified by the significant Valence x Incentive Magnitude interaction, $F(1, 43) = 12.27, p = .001$, indicating that participants responded faster after high reward cues than for the rest of the conditions.

The repeated-measures ANOVA for hits also showed significant main effects of valence, $F(1, 43) = 15.65, p < .001$, and incentive magnitude, $F(1, 43) = 9.24, p = .004$, but the effect for the Valence x Incentive Magnitude interaction did not reach significance ($p > .1$). Post hoc analyses indicated that the percentage of hits was higher for high than for low incentive cues and for reward than for punishment cues.

Results of Pearson correlations and partial correlations between SR scores and performance appear in **Table 1**. Only the correlation between SR scores and RTs for high incentive cues reached significance when the effect of low incentive cues was controlled, confirming that individuals with higher SR scores responded faster in high incentive conditions.

FMRI Results

Results from the overall task (see Figure 2) showed NAcc activation for both reward compared with punishment cues (right: 9, 12, 0; Z-score = 5.35; $p < .05$, FWE corrected; cluster size = 486 mm³; left: -9, 6, 0; Z-score = 3.97; $p < .05$, FWE corrected; cluster size = 405 mm³) and high incentive compared with low incentive cues (right: 15, 12, -6; Z-score = 4.07; $p < .05$, FWE corrected; cluster size = 270 mm³). In addition, the midbrain was activated in response to high incentive cues compared with low incentive

cues (-6, -21, -12; Z-score = 2.92; $p < .05$, FWE corrected; cluster size = 81 mm³). These results go along with previous studies that have shown midbrain response according to stimulus incentive magnitude (Knutson et al., 2005). Finally, the comparison of reward cues and the non-incentive cue showed activation in the bilateral NAcc (right: 9, 12, 0; Z-score = 6.57; $p < .05$, FWE corrected; cluster size = 999 mm³; left: -9, 6, 0; Z-score = 6.21; $p < .05$, FWE corrected; cluster size = 1,161 mm³) and midbrain (-3, -24, -9; Z-score = 4.09; $p < .05$, FWE corrected; cluster size = 378 mm³), accordingly with the greater response of these areas to high reward cues. Whole brain voxel-wise results from the overall task are summarized in supplementary material.

Effects of Reward Sensitivity on Task-Related Activations

Multiple regression analyses showed that SR scores correlated positively with right NAcc activation (12, 6, -6; Z-score = 3.20; $p < .05$, FWE corrected; cluster size = 108 mm³) and left midbrain activation (-3, -18, -15; Z-score = 4.07; $p < .05$, FWE corrected; cluster size = 135 mm³) for reward cues compared with punishment cues (see **Figure 3a**). Furthermore, SR scores did not correlate with activation in the ROIs for the comparison either between high incentive cues and low incentive cues, or between reward and non-incentive cues. Thus, these findings showed modulation of the NAcc and midbrain activation by reward sensitivity during reward processing, as shown in past reports (Carter et al., 2009; Hahn et al., 2009). Therefore, these ROIs were used for later PPI analysis as previously described (see Methods). No other positive or negative correlations were found.

PPI Results#

One-sample *t*-test analyses did not report any significant main effects (positive or negative) for any ROI. Nevertheless, we found that reward sensitivity modulated changes in connectivity among reward-related brain areas under incentive processing.

More specifically, we found a negative association between midbrain-mOFC connectivity and SR scores for high versus low incentive cues (0, 36, -15; Z-score = 3.73; $p < .05$, FWE corrected; cluster size = 297 mm³; **Figure 3b**). Thus, the connectivity between the midbrain and mOFC during incentive processing is dependent on individual differences in reward sensitivity. In order to study whether this effect was driven by reward or punishment cues, we performed two PPI analyses using high versus low reward cues and high versus low punishment cues separately as psychological variables. We did not observe any significant effect of SR scores for these two contrasts at predefined statistical thresholds. Thus, we may conclude that the reported effects are a result of the high incentive condition rather than driven by either of the valence conditions. Likewise, no positive or negative correlations with SR scores and brain connectivity were found regarding valence processing.

Additionally, analysis of connectivity when comparing reward cues and the non-incentive cue showed that connectivity between the NAcc and left amygdala was negatively associated with SR scores (-21, 0, -15; Z-score = 3.23; $p < .05$, FWE corrected; cluster size = 189 mm³; **Figure 3c**). This finding represents modulation of connectivity between the NAcc and left amygdala by reward sensitivity during the processing of reward cues compared with neutral cues.

Discussion

In this study, we have shown that individual differences in reward sensitivity modulate neural connectivity between the midbrain and mOFC during high incentive conditions, independently of the anticipation of possible high wins or losses. We also found that activity in the NAcc and midbrain is stronger for individuals with higher SR scores, which is consistent with previous reports (Carter et al., 2009; Hahn et al., 2009).

Crucially, our results showed that the trait of reward sensitivity modulates brain activity but also connectivity among reward-related brain regions.

In our study, SR scores were linked to increased activity in the NAcc and midbrain during the processing of reward cues compared with punishment cues. These results replicated those of a previous study using the MID task in which reward and punishment conditions were included (Carter et al., 2009). By contrast, contrary to our hypothesis, we did not find an association between NAcc response and SR scores for reward cues compared with neutral cues, an extension of results reported by Hahn (2009). One explanation for this negative result may be that the effects of individual differences in reward sensitivity on striatum activity were only driven by the motivation component of reward anticipation and not by its motor preparation component. That is, the anticipation of a motor response when a reward cue was present was not modulating the association between reward sensitivity and the NAcc, or at least not in the same direction. Thus, this result implies the importance of motivational contingencies in earlier behavioral studies in which RTs under reward conditioning were modulated by reward sensitivity (see Avila and Torrubia, 2008). Future studies targeting these interaction effects can better clarify the neural basis of modulation of motor or cognitive responses by reward sensitivity under reward cueing.

On the other hand, in a previous study, Hahn et al. (2009) used a modified version of the MID task in which only reward (not punishment) conditions were included and their results may have involved different contextual effects for modulation of the previously described brain activation by reward sensitivity (Patterson and Newman, 1993; Avila & Torrubia, 2008; Avila et al., 2008). Moreover, the difference in effects of reward sensitivity on NAcc activity between our research and Hahn et al.'s (2009) study may be related to previous findings with the MID task that demonstrated

NAcc modulation by available alternative incentives with the worst available alternative being an anchor for NAcc activation (Cooper et al., 2009). Therefore, modulation of dopaminergic activity by reward sensitivity during reward anticipation may be dependent on the referenced worst available alternative, inducing different contextual effects in different event designs. On the other hand, the NAcc has been involved in both approach and active avoidance behaviors (Salomone et al., 1997). Our results could be interpreted as primary modulation of the NAcc by reward sensitivity during approach anticipation compared with active avoidance, or as opposite modulation of the NAcc by reward sensitivity during approach and active avoidance behaviors. In future studies, it will be important to consider both contextual and condition effects to analyze how the reward sensitivity specifically modulates the response of the NAcc and midbrain to reward cues.

The crucial result of our study is that reward sensitivity modulates neural dynamics among reward brain areas. Higher SR scores were associated with relatively less connectivity between the midbrain and mOFC when processing high incentive cues. That is, activity of the midbrain during processing of high incentive cues seems to be more dependent on the mOFC in individuals with lower reward sensitivity. The mOFC is involved in processing reward outcomes (Haber & Knutson, 2010) and its lesion causes increased reward sensitivity (Bechara et al., 2000). Previous results with the MID task related the midbrain to the cue's incentive magnitude independent of its valence (Knutson et al., 2005). Overall, the caudal VTA might contribute to enhance learning in the novelty- and/or reward-processing contexts (Krebs et al., 2011). Animal studies have shown that the mOFC is implicated in the regulation of dopamine neuron activity (Aston-Jones et al., 2009; Overton et al., 1996; Tong et al., 1996, 1998) in that electrical stimulation of the OFC induces both inhibitory and excitatory responses in

dopamine neurons (Lodge et al., 2011). Specifically, Sesack et al. (2003) report that glutamatergic neurons from the prefrontal cortex target selectively in dopaminergic mesocortical neurons and in GABAergic mesoaccumbens neurons, suggesting that prefrontal cortex glutamatergic firing leads to inhibition of mesoaccumbens dopamine neurons, whereas prefrontal cortex hypofunction may promote subcortical dopaminergic transmission. Therefore, the effect of the mOFC on midbrain activity may reflect individual differences in reward sensitivity during the processing of high incentive stimuli. Moreover, we should note that cues involve reward and active avoidance anticipation, two processes that were suggested to be subserved by reward sensitivity and the Behavioral Activation System from the Reinforcement Sensitivity Theory. Further studies may contribute to clarifying the role of this coupling on the relevancy effect of salient stimuli and the maintenance of reward-seeking and active avoidance behavior in individuals with strong reward sensitivity (Takahashi et al., 2009).

On the basis of previous behavioral research on reward-response associations, we found that connectivity between the right NAcc and left amygdala during anticipation of reward cues was modulated by individual differences in reward sensitivity, involving motor preparation for response that correlated negatively with SR scores. This indicates that participants high in reward sensitivity displayed relatively less connectivity between the NAcc and amygdala when processing reward cues. The amygdala is a brain area composed of a group of nuclei involved in emotional learning and expression (Cardinal et al., 2002). Despite this area being classically linked to fear and anxiety processing, it is actually thought to play a more general role in encoding and updating the motivational and affective value of stimuli (Cardinal et al., 2002; Gottfried et al., 2003; Morrison & Salzman, 2010; Seymour & Dolan, 2008). The amygdala may contribute to goal-directed behavior through direct projections to the

NAcc as well as other regions of the striatum (Haber & Knutson, 2010; Friedman et al., 2002; Fudge et al., 2002) and through projections to dopaminergic areas in the midbrain (Cardinal et al., 2002; Pauli et al., 2012). This network is thought to be important for learning stimulus-reward associations (Everitt et al., 1989; Murray 2007; Pauli et al., 2012), and maintaining a representation of affective or rewarding properties of conditioned cues (Cardinal et al., 2002). Thus, lower connectivity between the NAcc and amygdala in individuals with greater reward sensitivity may represent lower flexibility in updating reward value. Consistent with this result, previous findings showed that amygdala lesions promote the selection of immediate rather than larger delayed rewards (Winstanley et al., 2004), reduce aversion to monetary loss (De Martino et al., 2010), increase risk choices under potential gains (Weller et al., 2007), and increase the selection of high-reward but ultimately high-punishment decks in the Iowa Gambling Task (Bechara et al., 1999). Thus, the amygdala seems crucial to appropriate decision making and its impairment may cause impulsive choices. Finally, the lack of modulation of NAcc-amygdala connectivity by reward sensitivity when comparing reward cues with punishment cues may be explained by the supposed role of the amygdala in processing both reward and punishment stimuli.

Limitations

A limitation of this study is inherent to the interpretation of PPI analyses. The PPI in itself is insufficient to assess the direction of effects. This is an important limitation considering, for example, the argued regulatory role of the mOFC and amygdala over the midbrain and NAcc respectively. Nonetheless, other studies, applying different methodologies, have provided more direct evidence for a top-down regulatory role in these networks (Aston-Jones et al., 2009; Overton et al., 1996; Tong et al., 1996, 1998; Stuber et al., 2011). On the other hand, the ROI definition of the

midbrain (6-mm sphere) may include nondopaminergic neurons in the region. We used this approach to study the midbrain due to the impossibility of uniquely selecting dopaminergic neurons of the VTA/SN complex in fMRI analyses. Likewise, it is important to note that the midbrain effects may not be exclusively mediated by dopamine neurons. Finally, we must be cautious with interpreting results in which the neutral condition was used as the control condition (i.e., NAcc-amygdala connectivity). These results may be driven by anticipation of incentive, preparation of motor responses for the attainment of objectives, or both. However, the neutral condition in this design did not involve a motor response for two reasons: First, preparation of motor responses was better controlled by the other incentive conditions, and second, the study had the secondary objective of analyzing modulation of reward-response anticipation by reward sensitivity. This was of particular interest given the trajectory of our research group (see Ávila & Parcet, 1997, 2001, 2002; Ávila et al., 2001, 2003) in that both processes involve the striatum (Guitart-Masip et al., 2011).

To summarize, in this study we have replicated previous findings showing that reward sensitivity modulates brain activity in the NAcc and midbrain. In addition, we have demonstrated that reward sensitivity also modulates connectivity of the midbrain and NAcc with the mOFC and amygdala respectively. Our results suggest that high reward sensitivity related activation in reward brain areas may partially result from associated diminished modulatory effects of other brain regions within the reward circuitry.

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Abbreviations

ANOVA: analysis of variance

fMRI: functional magnetic resonance imaging

FWE: family-wise error

MID: monetary incentive delay

MNI: Montreal Neurological Institute

mOFC: medial orbitofrontal cortex

PPI: Psychophysiological Interaction

ROI: regions of interest

RT: reaction time

SN: substantia nigra

SPM: Statistical Parametric Mapping

SR: Sensitivity to Reward

SVC: small volume correction

VTA: ventral tegmental area

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Tables

Table 1. Behavioral Results (N = 44)

Behavioral Result	Reaction Time (ms)		Hits (%)	
	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>
Overall Task	189.1	28.2	82.9	10.18
High Reward	184.87	24.27	86.83	10.51
Low Reward	191.08	31.06	82.67	13.65
High Punishment	191.06	31.37	82.19	9.98
Low Punishment	189.39	27.96	79.92	13.03
Correlation with SR Scores	Reaction Time		Hits	
Overall Task	$r = .172$		$r = .074$	
Valence Effect ⁺	$r = -.119$		$r = .060$	
Incentive Effect ⁺⁺	$r = -.331*$		$r = .030$	

M=mean; SD=standard deviation; ms=milliseconds; SR=Sensitivity to reward

The significant correlation at $p < .05$ (2-tailed) is presented in bold.

+ Partial correlation of reward cues' related variable controlled by punishment cues.

++ Partial correlation of high incentive cues' related variable controlled by low incentive cues.

There were no significant associations for each independent condition without taking into account the effects of lower level conditions.

Figure legends

Figure 1. Mean Reaction Times (RTs) and Accuracies During MID Task Completion for Each Condition

Left: mean RTs for each incentive condition. Right: percentage of hits for each incentive condition. Dark bars represent high incentive conditions and white bars represent low

incentive conditions. Post hoc analyses showed that the high-reward condition yielded a higher percentage of hits and lower RTs than the rest of the incentive conditions ($p < .05$).

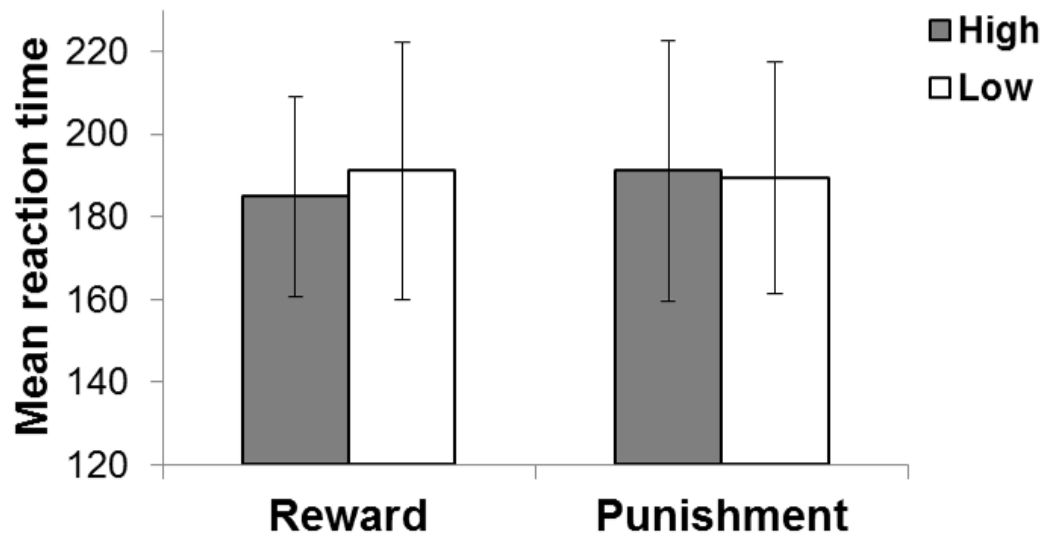
Figure 2. Mean Percent Signal Change for Each Condition Across All Voxels Within the Midbrain and NAcc ROIs

Dark bars represent high incentive conditions and white bars represent low incentive conditions.

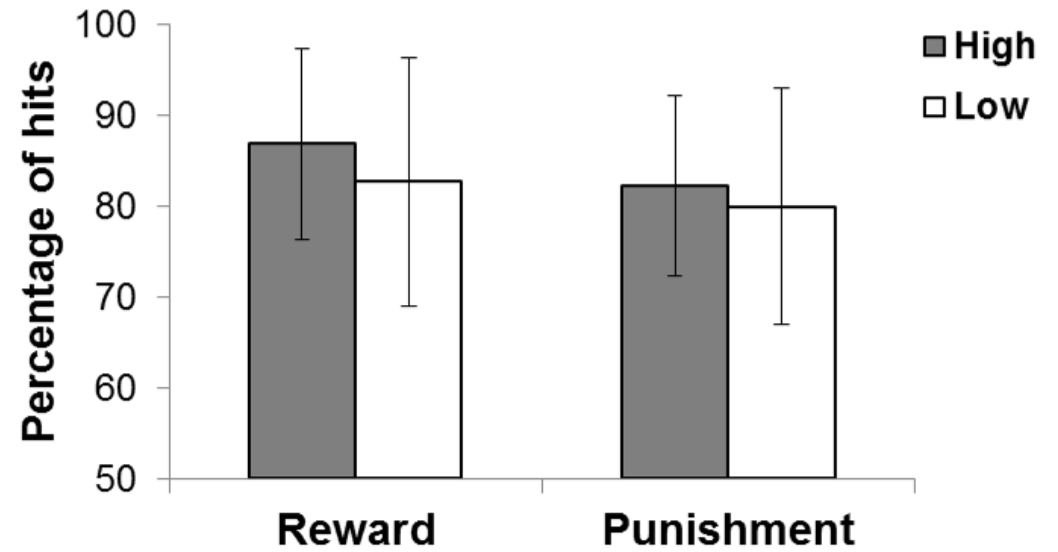
Figure 3. fMRI Results at $p < .05$ (FWE Corrected)

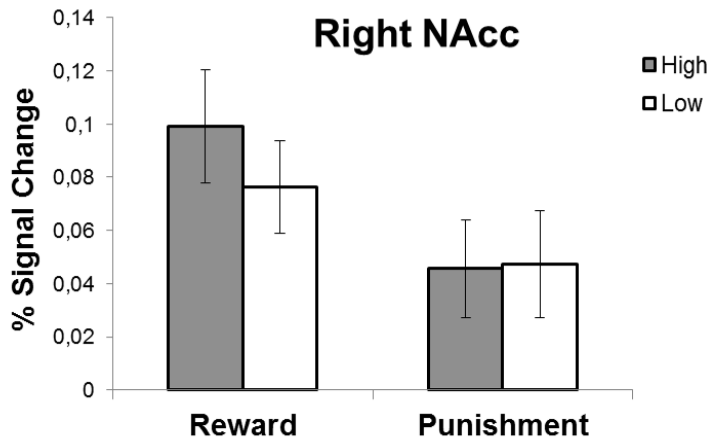
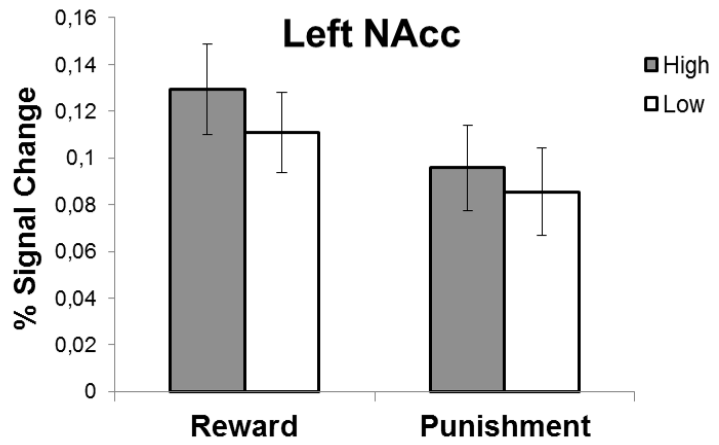
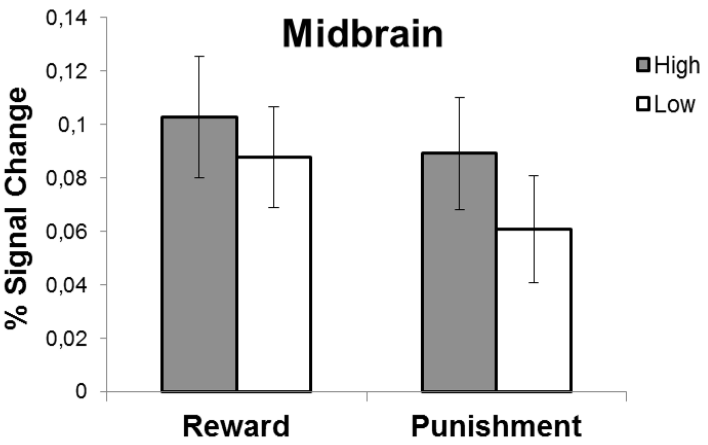
a) Left: brain regions (midbrain and nucleus accumbens [NAcc]) showing positive correlation with Sensitivity to Reward (SR) scores during reward anticipation compared with punishment anticipation. Right: scatterplots of mean cluster activity within the regions of interest (midbrain and NAcc) and SR scores. b) Left: resulting image of the psychophysiological interaction (PPI) analyses for high compared with low incentive cues using the midbrain as a source region and SR scores as a regressor. Right: scatterplot of mean cluster weights for the interaction term in the medial orbitofrontal cortex and SR scores. c) Left: resulting image of the PPI analyses for reward compared with neutral conditions using the right NAcc as a source region and SR scores as a regressor. Right: scatterplot of mean cluster weights for the interaction term in the amygdala and SR scores. Images are presented in neurological convention (left is left). The color bar represents the t values applicable to the image.

Reaction Time



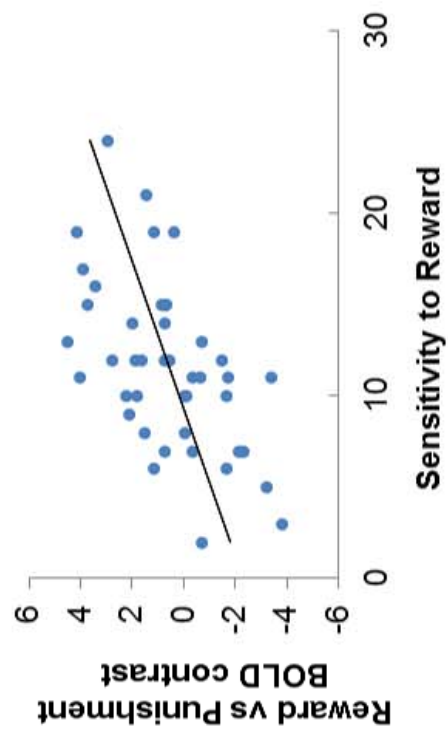
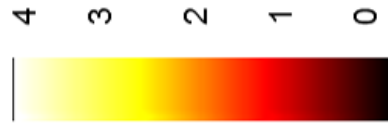
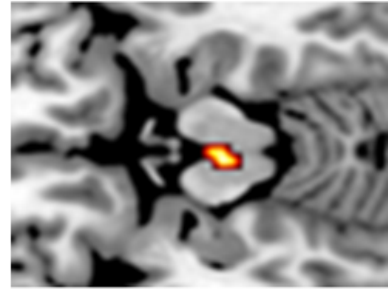
Hits



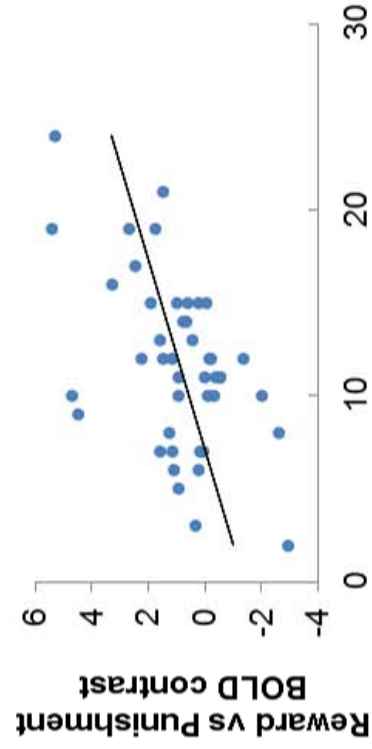
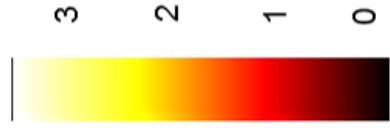
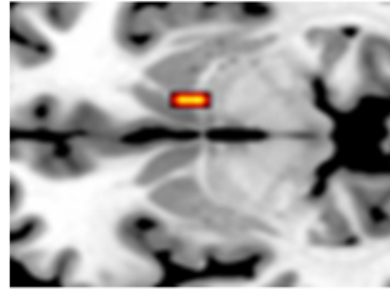


a)

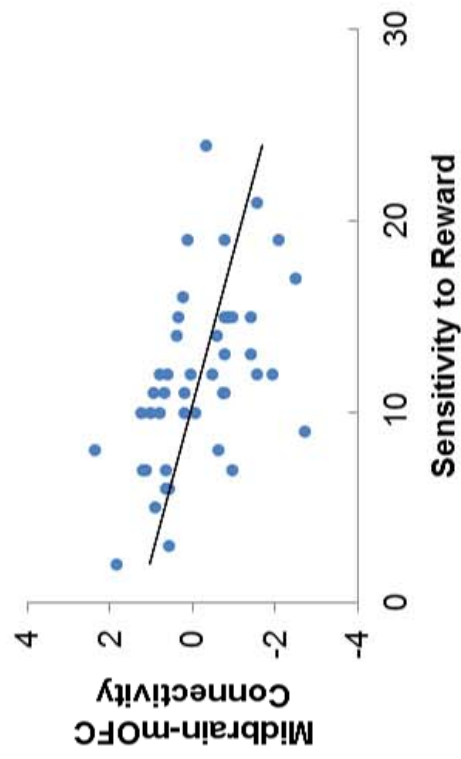
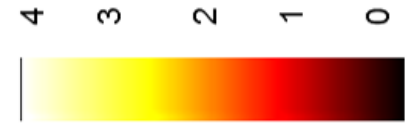
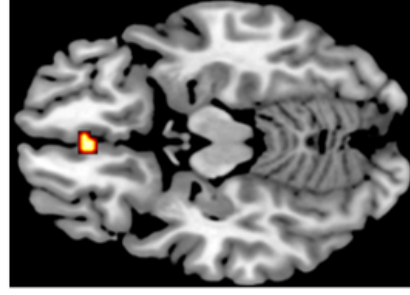
Midbrain



NAcc

**b)**

mOFC

**c)**

Amygdala

