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FMRI Visualization of Brain Activity during a Monetary Incentive Delay Task

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Comparative studies have implicated striatal and mesial forebrain circuitry in the generation of autonomic, endocrine, and behavioral responses for incentives. Using blood oxygen level-dependent functional magnetic resonance imaging, we sought to visualize functional activation of these regions in 12 normal volunteers as they anticipated and responded for monetary incentives. Both individual and group analyses of time-series data revealed significant activation of striatal and mesial forebrain structures (including insula, caudate, putamen, and mesial prefrontal cortex) during trials involving both monetary rewards and punishments. In addition to these areas, during trials involving punishment, group analysis revealed activation foci in the anterior cingulate and thalamus. These results corroborate comparative studies which implicate striatal and mesial forebrain circuitry in the elaboration of incentive-driven behavior. This report also introduces a new paradigm for probing the functional integrity of this circuitry in humans.

Key Words: **incentives; reward; punishment; monetary; caudate; putamen; thalamus; anterior cingulate; mesial prefrontal cortex; FMRI; human.**

Animals' survival depends on their ability to predict and respond to incentives. Specifically, anticipation of reward should facilitate approach behavior while anticipation of punishment facilitates avoidance (Young, 1959). In the case of humans, it is likely that these critical skills depend upon the functional integrity of an evolutionarily conserved brain substrate. Comparative research suggests that midbrain nuclei modulate the activity of subcortical and cortical brain structures responsible for anticipating and responding for incentives (MacLean, 1990; Panksepp, 1998).

Few human studies have directly assessed the impact of incentive cues on activity in brain regions which lie below the cortex (Davidson and Irwin, 1999). While one positron emission tomography (PET) study found increased blood flow in orbital and dorsolateral prefrontal cortex as well as thalamus during a monetarily rewarded task (Thut *et al.*, 1997), another PET study revealed increased raclopride displacement (indicative of dopamine release) in striatal forebrain areas during a videogame task (Koepp *et al.*, 1998). Similarly, in a published abstract using functional magnetic resonance imaging (FMRI), investigators reported increased oxygenation of the striatum during presentation of a tone cue associated with monetary reward (Breiter *et al.*, 1996). Because of its superior spatiotemporal resolution, we used FMRI to address whether monetary incentives could increase activity in striatal and mesial prefrontal circuitry. We also examined whether trials involving potential monetary reward versus potential monetary punishment might recruit different components of this circuitry.

Our hypotheses came from research on nonhuman primates. Depth electrode studies indicate that anticipation of food or liquid reward activates dopaminergic neurons in the ventral tegmental area (VTA) of the midbrain (Schultz *et al.*, 1997). In humans, VTA neurons project rostrally, targeting striatal (i.e., nucleus accumbens, caudate, putamen), limbic (i.e., olfactory areas, lateral septum, amygdala), and paralimbic regions (i.e., piriform cortex, entorhinal cortex, anterior cingulate, and mesial prefrontal cortex) (Garris *et al.*, 1993; Nieuwenhuys, 1985). Since the VTA is relatively small and basal in the brain, and thus difficult to resolve with current FMRI technology, we focused our hypotheses on these VTA terminal regions.

A medially located subset of these VTA targets (i.e., nucleus accumbens, caudate, putamen, anterior cingulate, and mesial prefrontal cortex) has been implicated in anticipating and responding to incentives. Neuroanatomical tracing studies show that the paralimbic aspects of these projections also receive massive inputs from other related cortical regions. For example, the mesial prefrontal cortex receives afferents from much of the rest of the prefrontal cortex (Tanji, 1994). The output of the mesial prefrontal cortex then projects directly to supplementary motor area, hypothalamus, and periaqueductal gray of the brain stem (An *et al.*, 1998; Ongur *et al.*, 1998). As a result, the mesial pre-

frontal cortex might provide modulated cortical control over coordinated components of incentive response, including motor preparedness, endocrine tone, and autonomic arousal (Price, 1999). Thus, dopaminergic modulation of the mesial prefrontal cortex should facilitate approach behavior, which constitutes an adaptive response to potential reward (Ikemoto and Panksepp, 1999). On the basis of these comparative findings, we predicted that anticipation of and response for reward would activate striatal and mesial forebrain targets of the VTA.

To date, comparative studies have shown less consistency in demonstrating whether VTA dopaminergic projections play a central role in the anticipation of as well as active avoidance of punishment. Primate single-unit studies have demonstrated that VTA dopaminergic neurons decrease firing when an expected reward fails to occur (Mirenowicz and Schultz, 1996). However, studies in rats suggest that acute escapable stressors (i.e., tail pinch or foot shock) can increase dopaminergic firing in the striatum and mesial forebrain (Ravard *et al.*, 1990; Salomone, 1994). Therefore, we investigated whether trials involving escapable punishment would activate the same regions implicated in trials involving reward.

MATERIALS AND METHODS

With monetary incentives, we invoked anticipation of reward and punishment in normal volunteers. Using FMRI, we scanned participants' brains during trials in which they anticipated potential monetary reward, punishment, or no consequences. Participants' monetary outcome depended on their performance on a simple reaction time task at the end of each trial which involved pressing a button during the brief presentation of a visual target. We then applied regression analyses to individual and grouped time series data to contrast activation during incentive (i.e., reward or punishment) versus nonincentive (i.e., neutral) trials.

Participants

Twelve right-handed males participated (mean age 26, SD 3.9; Edinburgh Handedness Inventory >44). Three additional participants were eliminated from the analysis because of excessive head motion during the scan. We verified that all participants were free of neurological disorders, medical disorders, HIV, and concurrent medications or drugs of abuse via a physical examination which included blood and urine tests. A psychiatric interview (SCID for DSM III-R, NP) ensured that none had a history of Axis I disorders or substance abuse (including alcohol abuse or dependence). Radiologists also judged participants to be free of brain abnormalities on the basis of high-resolution structural magnetic resonance images. All participants gave written informed consent, and the study was approved by the Human Subjects Review Board of the National Institute on Alcohol Abuse and Alcoholism.

Procedure

After screening, participants completed a simple reaction time task during which their mean reaction time was recorded for standardization of later experimental tasks. Next, participants completed standardized questionnaires (data not presented here) and practiced the experimental tasks. Before going into the scanner, the experimenter showed participants the money they could earn by performing the experimental tasks successfully while in the scanner (all participants correctly believed that they would receive this cash at the end of the experiment). Finally, participants entered the scanner and structural and functional scans were collected. As functional scans were acquired, participants engaged in the experimental tasks.

Incentive Tasks

During functional scans, participants engaged in three consecutive tasks involving either no monetary outcome ("control task"), potential reward ("reward task"), or potential punishment ("punishment task"). The reward task was modeled after a reward incentive delay task which was designed to elicit firing of VTA dopamine neurons in monkeys (Schultz *et al.*, 1998). We presented incentive trials singly (i.e., not in blocks) and at unpredictable intervals (i.e., in a pseudorandom sequence). Thus, our experimental design was similar to aperiodic "event-related" designs described by other investigators (Buckner, 1998). Participants completed the practice task first and then the reward and punishment tasks in counterbalanced order.

Each task consisted of 100 6-s trials (10 min total). During each trial, participants saw a colored square (cue; 500 ms), waited a variable interval (delay; 4000–4500 ms), and then responded to a white target square which appeared for a variable length of time (target; 160–260 ms) with a button press. Immediately after the response, feedback appeared (feedback; 500 ms) documenting whether the participant had won or lost money as well as their cumulative sum total at that point. Each trial included two FMRI volume acquisitions lasting 3 s each. The first volume was acquired during the delay period and was time locked to the offset of the cue. The second volume was acquired during the combination of response, feedback, and presentation of the cue for the next trial (see Fig. 1). Each task included two types of trials, as described below:

(1) Control task: Participants received no money at the beginning of this task and were told that they would neither win nor lose money based on their performance, but that their reaction times would be re-

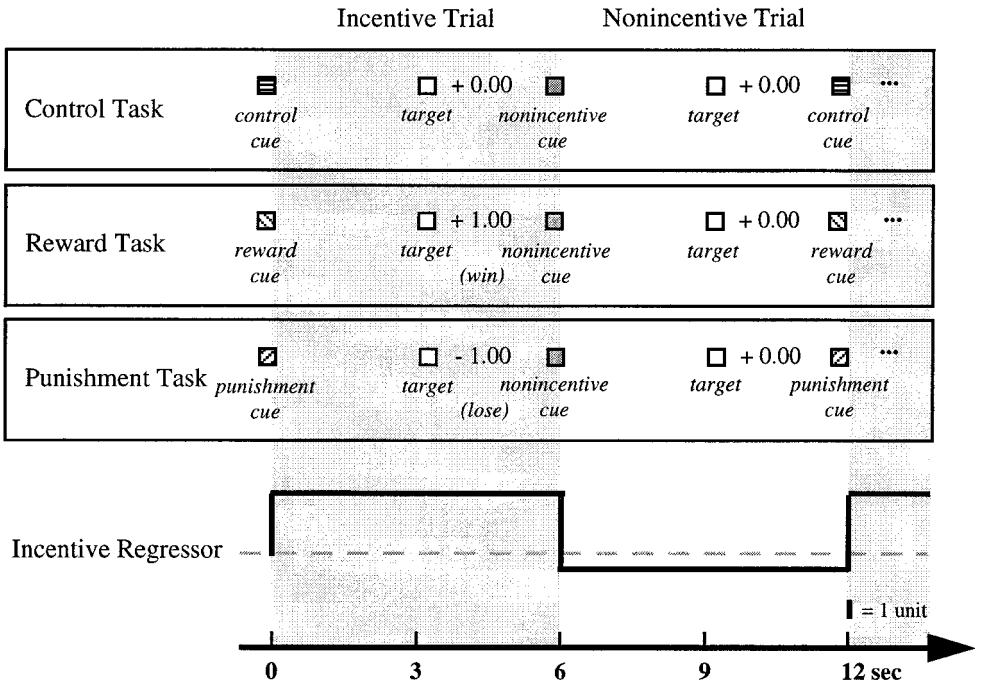

FIG. 1. Task design and regressor. The regressor represents the contrast of incentive versus nonincentive trials for each task. The control task regressor constitutes a sensory control for the incentive task regressors.

corded throughout the task. Each trial was signaled by either a red cue (20 trials) or a green cue (80 trials). Trials were presented in a pseudorandom order, with the stipulation that red-cued trials could not occur consecutively (these stimulus presentation parameters matched those of both the reward and the punishment tasks described below).

(2) Reward task: Participants received no money at the beginning of the task and were told that their goal was to make money. Additionally, they were informed: (1) on trials signaled by an orange cue (20 trials), if they responded during presentation of the subsequent white target, they would earn $1.00; (2) on trials signaled by the blue cue (80 trials), their performance would not affect their total, but they should do their best anyway; (3) reaction time would be recorded on all trials. Trials were presented in a pseudorandom order, with the stipulation that orange-cued (i.e., reward) trials could not occur consecutively.

(3) Punishment task: Participants received $20.00 at the beginning of the task and were told that their goal was to avoid losing money. Additionally, they were informed: (1) on trials signaled by a yellow cue (20 trials), if they failed to respond during presentation of the subsequent white target, they would lose $1.00; (2) on trials signaled by a pink cue (80 trials), their performance would not affect their total, but they should do their best anyway; (3) reaction time would be recorded on all trials. Trials were presented in a pseudorandom order, with the stipulation that yellow-cued (i.e., punishment) trials could not occur consecutively.

Incentive task difficulty was calibrated to participants' mean reaction time (collected before entering the scanner), so that each participant succeeded on approximately 60% of the incentive trials (mean success rate 61.7%, SD 10.65). Cue colors were counterbalanced for each task in a pilot study and found not to differentially affect brain activation in any of the regions under investigation. Stimuli were presented, responses were recorded, and feedback was calculated by Gentask software (NeuroScan, El Paso, TX) running on a personal computer platform (IBM, Armonk, NY). Stimuli were backprojected onto a translucent screen placed at the foot of the participant with a magnetically shielded liquid crystal display video projector (InFocus, Wilsonville, OR). Participants viewed the screen from inside the magnet bore via an angled reflecting mirror system.

Imaging Procedure

Images were acquired with a 1.5-T Signa magnet (General Electric, Milwaukee, WI) utilizing a standard quadrature head coil. Interleaved multislice BOLD T2*-weighted gradient echoplanar imaging was used to produce 10 contiguous 7-mm-thick coronal slices spanning the corpus callosum and caudally delimited by the inferior colliculus [field of view 24 cm; repetition time (TR) 3000 ms; echo time (TE) 35 ms; flip angle 90°; 64 × 64 matrix of 3.75-mm^2 voxels] (see Fig. 1). High-resolution T1-weighted images were acquired coronally at the same locations as the echo planar images

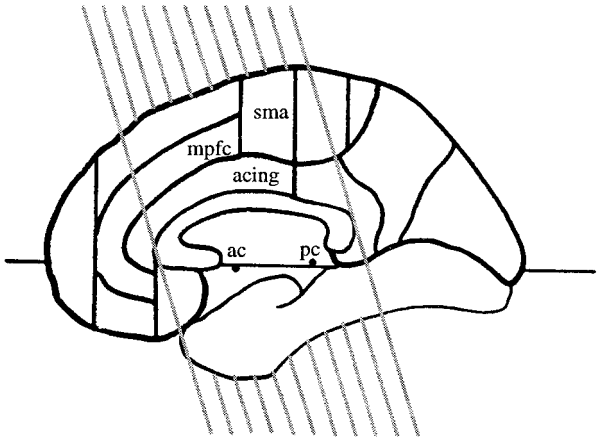

FIG. 2. Midline volumes of interest and slice placement. Gray lines represent placement of coronal slices. Volumes of interest along the medial prefrontal wall include the anterior cingulate (acing), mesial prefrontal cortex (mpfc), and supplementary motor area (sma). The mpfc is delimited posteriorly by a vertical line extending through the anterior commissure (ac); acing and sma are delimited posteriorly by a vertical line extending through the precentral sulcus. The acing is delimited ventrally by the corpus callosum and dorsally by the cingulate sulcus, while mpfc is delimited dorsally by the paracingulate sulcus (Rademacher *et al.*, 1992).

(TR 100 ms; TE 7 ms; flip angle 90°) so as to provide detailed anatomical information for the individual analyses. A second set of high-resolution structural scans of the whole brain was acquired in the axial plane for coregistration of statistical maps and warping to Talairach space.

Analysis

After reconstruction, voxel time series were interpolated (using sinc interpolation and the most anterior slice as a reference) to correct for nonsimultaneous slice acquisition within each volume. Data were then corrected for three-dimensional motion after which means and linear trends were removed with Analysis of Functional Neural Images (AFNI) software (Cox, 1996). Visual inspection of registration graphs confirmed that no participant's head had moved more than 1.5 mm in any dimension from one volume acquisition to the next or more than 3 mm over the course of any task. Three participants whose head movement violated this threshold were eliminated from the analysis, leaving a total of 12 participants.

Image time series data were analyzed with multiple regression (Petit *et al.*, 1998) (see Fig. 2). A regressor was constructed to contrast blood oxygen level-dependent (BOLD) signal during incentive trials versus nonincentive trials within each task (hereafter referred to as "activation," see Fig. 1). Prior to analysis, the regressor was convolved with a model of the hemodynamic response (Cox, 1996).

Individual Analyses

Statistical maps corresponding to the regressor were calculated for each task, yielding a total of three statistical maps per participant (see Fig. 1). The statistical map for the control task could be considered a sensory control for the statistical maps of the reward and punishment tasks, since it modeled identical stimulus characteristics which lacked differential incentive value (although this interpretation must be tempered by the fact that the control task always occurred first). All statistical maps were initially calculated as T statistics and then transformed into Z scores.

Based on the hypotheses and anatomical limits of our scanning range, we selected 11 volumes of interest (VOIs), including right and left nucleus accumbens, right and left caudate, right and left putamen, thalamus, midline anterior cingulate, midline mesial prefrontal cortex, midline supplementary motor area, and left motor cortex (see Fig. 2). For a representative participant's brain, the total voxel count in these VOIs summed to approximately 500 ($\sim$50,000 mm^3). Bonferroni correction of a $P = 0.05$ criterion for 500 comparisons yielded a corrected criterion of $P = 0.0001$ ($Z = 3.88$, two-tailed). Voxels passing this threshold in each individual's maps were highlighted. The thresholded maps were coregistered with high-resolution structural brain images which were obtained immediately prior to the functional scans and were used to specify the location of functional scan acquisition. Using the structural images to locate anatomical landmarks, coders counted the number of highlighted voxels within each VOI (Constable *et al.*, 1998). Boundaries of subcortical VOIs were established according to the criteria set forth by Breiter and colleagues (1997), while boundaries of paralimbic VOIs along the medial wall were delineated according to the criteria described by Rademacher and colleagues (1992) (see Fig. 2). Within each participant, VOI thresholded voxel counts in the incentive maps were compared with counts in the control maps using Wilcoxon matched-pair tests. The following statistical comparisons were made: (1) reward versus sensory control and (2) punishment versus sensory control. We predicted that participants would show VOI activation in both reward and punishment maps versus the sensory control map. For descriptive purposes, we computed the sample-wide prevalance of activation for each VOI using percentages (LaBar *et al.*, 1998). Mann–Whitney tests revealed no significant effects of order on activation in any VOI for the incentive tasks, so we did not include order as a factor in any of the following analyses.

Group Analyses

Group analyses were conducted to visualize and verify the patterns of activity observed in individual analyses. First, both statistical maps and structural scans

TABLE 1

Individual VOI Activation Prevalence (>33%, $P < 0.0001$) and Within-Subject Comparisons

Area (Brodman's area)	Reward %	Punishment %
R nuc accumbens		
L nuc accumbens		
R caudate	50	50
L caudate	42	67
R putamen	42	58
L putamen		33
Thalamus	50	58
Ant cingulate (24)	42	50
Mes prefrontal ctx (32)	92	83
Sup motor area (6)	33	42
L motor ctx (4)	83	50

were aligned to the anterior and posterior commissures and transformed into the standard stereotactic Talairach space (Talairach and Tournoux, 1988) using AFNI. Then, resampled (1 mm^3) statistical maps were smoothed slightly (RMS = 4 mm) and combined via a meta-analytic formula to derive group maps for each regressor. Specifically, Z maps were summed and divided by the square root of the number of subjects (Beauchamp *et al.*, 1999). Since the original voxel size had been approximately recaptured by smoothing, we applied the same threshold used in individual maps to group maps (i.e., $Z = 3.88$, $P < 0.0001$). As with individual analyses, separate thresholded activation maps were constructed for the control, reward, and punishment regressors.

RESULTS AND DISCUSSION

We predicted that trials involving reward would activate striatal and mesial forebrain structures enervated by dopamine terminals (see Table 1). We also hypothesized that these regions might be activated by trials involving punishment.

Individual Analyses

As expected, no significant activation was observed in any VOI in any participant for the control task maps. As seen in Table 1, most of the predicted striatal and mesial forebrain regions showed significant incentive-related activation in most participants. Specifically, a majority of participants showed significant reward map activation relative to the sensory control in the caudate, thalamus, mesial prefrontal cortex, and left motor cortex. In addition to these areas, analysis of the punishment maps also revealed significant activation of the putamen and anterior cingulate in most participants.

Group Analyses

No voxels in the VOIs exceeded the threshold in the control group map, but predicted patterns of activation observed in individual analyses emerged for both re-

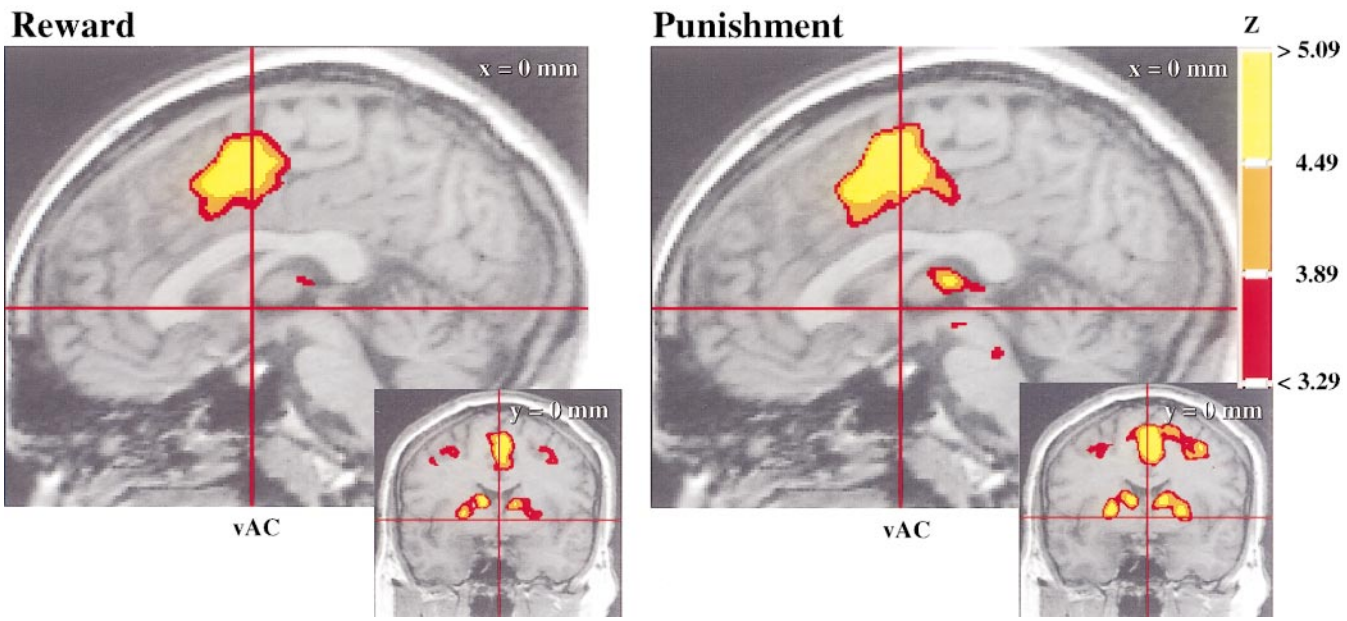

FIG. 3. Group maps for incentive tasks. Color-coded averaged Z-score maps illustrating reward- and punishment-related activity combined for 12 participants ($Z = 3.88$; $P < 0.0001$) are shown overlaid onto Talairach normalized anatomical magnetic resonance images. Sagittal slices are depicted at midline and coronal slices are depicted at the anterior commissure (AC). As per radiological convention, right is on the left and left is on the right.

TABLE 2

Group VOI Maximum *Z* Scores and Talairach Coordinates of Activation Foci ($P < 0.0001$, $n = 12$)

	Reward		Punishment	
Area (Brodman's area)	Max *Z*	TC (R, A, S)	Max *Z*	TC (R, A, S)
R ant insula (13)	4.43	33, 16, 6	3.67	32, 20, 4
L ant insula (13)			3.94	−27, 21, 4
R nuc accumbens				
L nuc accumbens				
R caudate	5.40	10, 1,12	5.36	11, 3,10
L caudate	4.81	−10, 4, 9	5.62	−10, 5, 8
R putamen	4.75	23, 1, 4	5.31	22, 1, 5
L putamen	3.96	−23,−3, 4	5.11	−20, 4, 3
Thalamus			4.74	−5,−17, 9
Ant cingulate (24)			4.64	4, 14,32
Mes prefrontal ctx (32)	7.43	−1, 5,44	7.49	−1, 5,45
Sup motor area (6)				
L motor ctx (4)	4.50	−37,−9,43	4.68	−31, −1,44

ward and punishment group maps ($n = 12$, see Fig. 3). For the reward group map, activated areas included caudate, putamen, mesial prefrontal cortex, and left motor cortex. The punishment group map also revealed activations in these areas, as well as thalamus and anterior cingulate. Maximum activation values and Tailarach coordinates (TC) for VOIs in these combined maps are listed in Table 2. Interestingly, at an exploratory threshold ($P < 0.001$), group maps further revealed activations of lower midbrain foci approximately corresponding to the location of the ventral tegmental area/substantia nigra (max $Z = 3.44$; TC −1, −18, −6) and locus coeruleus (max $Z = 3.57$; TC −2, −31, −14) for punishment trials, but not for reward trials (see Fig. 3).

Several factors suggest that we were able to unmask incentive-related brain activity with the current paradigm. First, the observed activations could not be accounted for by unique sensory qualities of the stimuli accompanying the incentive trials, since a stimulus train in the control task with identical properties to the reward and punishment stimulus trains in the incentive tasks failed to elicit significant activation in any participant. This comparison controls for the possibility that objective features of the incentive stimulus trains induced activation in participants (e.g., via novelty or oddball effects due to aperiodic presentation). Only when paired with incentive value did these stimuli elicit activation. Second, the mere invocation of motor preparation could not account for the findings. Participants responded on all trials, yet the observed patterns of activation were specific to incentive trials. Third, we minimized expectancy and habituation effects by presenting incentive trials singly and aperiodically, rather than blocked together, so that participants could not predict whether consecutive trials would involve incentives. If VTA dopamine neurons fire more readily to cues which predict potential reward than to reward delivery per se (Schultz *et al.*, 1997), then this design should have enhanced the visibility of that signal relative to traditional blocked designs.

Despite the confirmatory nature of the findings, we faced a technological limitation that will be remedied in future studies. Due to constraints on scanner memory, we were able to collect data encompassing only the midsection of the brain, an area which included the volumes of interest, but omitted more rostral forebrain structures which may also play critical roles in incentive appraisal (Price, 1999). Future studies with whole-brain acquisition will remedy this shortcoming. Also, although we observed activation in most of the hypothesized striatal regions, we did not observe significant activation of the nucleus accumbens. Part of this absence may stem from a combination of stringent significance thresholds and small BOLD signals typically obtained in subcortical regions. However, it is also possible that our statistical model lacked sufficient temporal resolution to capture potentially phasic signals in the nucleus accumbens. For instance, *in vivo* cyclic voltammetry studies of rats suggest that nucleus accumbens shows greatest activity during appetitive rather than consummatory phases of reward conditioning (Garris *et al.*, 1999; Richardson and Gratton, 1996). Thus, future FMRI studies may better resolve nucleus accumbens activity by combining regionally constrained hypotheses with statistical models which focus on anticipatory periods.

One strength of our paradigm is that it allowed us to compare neural responses during trials which involved financially equivalent rewards and punishments. Group analyses suggested that both types of trials evoked similar patterns of activation. For instance, both elicited the predicted activation of striatal areas such as the caudate and putamen, which have been implicated in preparation for behavioral responses for incentives (Schultz *et al.*, 1998). Additionally, both types of incentive trials robustly activated the mesial prefrontal cortex (BA 32; also labeled "anterior cingulate" and "pre-SMA" by others). The psychological function of this region remains somewhat mysterious. Unlike the supplementary motor area (SMA) which lies behind it, activity in this area is not clearly tied to specific movements (Tanji, 1994). For example, unlike the SMA, electrical stimulation of this area can elicit a sense of impending movement or "urge" to move in humans but not movement itself (Fried *et al.*, 1991). Also, a PET investigation found increased oxygen utilization in this area during anticipatory intervals, regardless of what kind of response ensued (e.g., manual or verbal) (Murtha *et al.*, 1996). Other PET studies have shown that activity in this region covaries with skin conductance, in the context of both aversive and

nonaversive visual stimuli (Fredrikson *et al.,* 1998). Since incentive trials preferentially activated this area, while behavioral demands remained constant across trials, it is possible that this area stores incentive information online in a kind of working memory buffer, which may or may not influence later behavior.

Despite the apparent similarity of the activation patterns elicited by reward and punishment trials, group analyses also suggested some differences. Specifically, group maps revealed activation foci in right anterior cingulate and thalamus for punishment but not reward trials. Additional recruitment of these areas in response to potential monetary loss accords well with FMRI studies which show activation of these same areas in response to cues which predict such other aversive outcomes such as noise blasts (Buchel *et al.*, 1999) and electrical shocks (Ploghaus *et al.*, 1999). However, more research is needed to determine whether this discriminant result replicates in other samples and whether it results from local changes in brain activity or the modulatory influence of distal midbrain nuclei. Indeed, exploratory analysis also suggested preferential activation of the locus coeruleus during punishment trials, which might have a modulatory effect on the activation of some of these areas.

Finally, visual inspection of the activation maps revealed some incentive-related activations which did not fall within the predicted VOIs. Specifically, both group reward and punishment maps revealed activation foci within the anterior insula. These observations may have functional significance, since the anterior insula has been implicated in visceral responses to emotional stimuli (Cechetto and Saper, 1990). For the sake of completeness, we have listed these foci of activation in Table 2. However, since these observations were not based on prior hypotheses, they cannot be regarded as statistically significant. Verification of these findings awaits future replication.

In conclusion, FMRI enabled us to visualize the activation of striatal and mesial prefrontal circuitry putatively involved in assessment of and response for incentives. Although BOLD FMRI provides an indirect index of brain oxygenation rather than a measure of dopaminergic activity, our findings are consistent with the hypothesis that midbrain dopaminergic neurons may have contributed to the regionally specific patterns of activation that we observed. Future investigations may focus on the time course and functional correlates of activation of this circuitry. In addition to these findings, we introduce a method for eliciting anticipation of comparable positive and negative monetary outcomes within the FMRI environment.

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