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Striatal dopamine transmission in healthy humans during a passive monetary reward task

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Research on dopamine (DA) transmission has emphasized the importance of increased phasic DA cell firing in the presence of unpredictable rewards. Using [^{11}C]raclopride PET, we previously reported that DA transmission was both suppressed and enhanced in different regions of the striatum during an unpredictable reward task [Zald, D.H., Boileau, I., El Dearedy, W., Gunn, R., McGlone, F., Dichter, G.S. et al. (2004). Dopamine transmission in the human striatum during monetary reward tasks. J. Neurosci. 24, 4105–4112]. However, it was unclear if reductions in DA release during this task reflected a response to the high proportion of nonrewarding trials, and whether the behavioral demands of the task influenced the observed response. To test these issues, we presented 10 healthy subjects with an automated (passive) roulette wheel game in which the amount of reward and its timing were unpredictable and the rewarding trials greatly outnumbered the nonrewarding ones. As in the previous study, DA transmission in the putamen was significantly suppressed relative to a predictable control condition. A similar suppression occurred when subjects were presented with temporally unpredictable novel pictures and sounds. At present, models of DA functioning during reward do not account for this suppression, but given that it has been observed in two different studies using different reward paradigms, this phenomenon warrants attention. Neither the unpredictable reward nor the novelty conditions produced consistent increases in striatal DA transmission. These data suggest that active behavioral engagement may be necessary to observe robust statewise increases in DA release in the striatum.

Introduction

Research in animals has emphasized the importance of increased dopamine (DA) cell firing in the presence of unpredictable rewards (Schultz, 2001). However, direct data on DA release in humans in relation to predictability remain limited. Some investigators have attempted to use blood oxygen level-dependent (BOLD) fMRI in the striatum as an index of DA activity (Knutson and Gibbs, 2007), but this technique is at best an indirect indicator of DA activity. Measurement of the radiolabeled D_2 ligand [^{11}C]raclopride with positron emission tomography (PET) provides a more direct assessment of DA functioning. Because the binding potential (BP) of [^{11}C]raclopride is inversely related to endogenous DA release, changes in [^{11}C]raclopride's BP across task conditions can be used to index statewise changes in DA release (Laruelle, 2000). Increased DA transmission has been observed during several behavioral paradigms including playing an engaging video game (Koepp et al., 1998), exposure to highly palatable food (Small et al., 2003), exposure to drug cues in drug addicts (Volkow et al., 2006), during a psychosocially stressful math task (Pruessner et al., 2004), during painful stimulation (Scott et al., 2006), and during placebo administration of analgesics (Scott et al., 2007) and psychostimulants (Boileau et al., 2007).

In previous research (Zald et al., 2004), we reported both enhancement and suppression of DA release in different parts of the striatum during an unpredictable reward task. Whereas the increased DA release in the caudate was consistent with predictions from animal research, suppression of DA release in the putamen was unexpected. The DA suppressions emerged in the putamen in contrasts between unpredictable and predictable reward conditions, which suggests that the unpredictable aspect of the reinforcement contingency critically contributed to the modulation of DA. However, interpretation of these data is complicated for two reasons. First, the unpredictable reward condition possessed a high percentage of nonreward trials, whereas in the predictable reward condition no predicted rewards were ever withheld. Given that withholding of expected rewards causes transient suppression of DA cell firing in monkeys (Schultz, 2001), it seems reasonable that these nonreward trials might have contributed to the reduced DA release. Second, although all conditions required similar movements, it is possible that there was an interaction between the reward contingency and the required motor responses, since motor

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demands have been found to influence striatal responses in fMRI studies (Elliott et al., 2004; Bjork and Hommer, 2007). To clarify these interpretational issues, we ran subjects on a new unpredictable reward task in which rewards were unpredictable in terms of both value and timing. To rule out any motor interactions, the task was presented in a passive form that required no response from the subject.

The current study also extends previous research by examining whether novel but nonrewarding stimuli elicit DA responses, as indicated by animal experiments (Horvitz, 2000;Legault and Wise, 2001). To test whether similar effects emerge in humans, and to see how these effects compare to monetary reward, we additionally had participants complete a task in which temporally unpredictable novel visual and auditory stimuli were presented using a passive paradigm that was otherwise identical to the monetary reward task. The use of the novel condition also provides a further test of the sensitivity of the [^{11}C]raclopride technique, in that to date it has not been clear whether it is possible to use this technique to detect DA responses to sensory stimuli that lack strongly motivating properties. Therefore, all participants underwent three PET scanning sessions: (1) unpredictable monetary reward, (2) novel stimulation, and (3) sensorimotor control.

Materials and methods

Subjects

Twelve healthy right-handed male subjects, mean age 25 (±0.9), participated in the study. All subjects were free of current or past medical or psychiatric illness. All subjects completed written informed consent approved by the Montreal Neurological Institute ethics committee and the Vanderbilt University Institutional Review Board.

Study design and procedure

Subjects meeting inclusion criteria for the study were scheduled to participate in the three [^{11}C]raclopride PET scanning sessions. The three conditions were counterbalanced across subjects, with each task occurring during separate scan sessions that were at least 24 h apart. The tasks started approximately 15 min before tracer injection and lasted 30 min. To control for diurnal variations in DA function, all subjects were tested at the same time of day. Subjects arrived at the PET unit 90 min before the injection of 7 mCi of [^{11}C]raclopride. Twenty minutes prior to tracer injection, an intravenous catheter was inserted into the subject's arm. Baseline behavioral (mood, alertness) and physiological (systolic and diastolic blood pressure, heart rate) measures were taken 20 min before injection.

Stimulation paradigm

The stimulation paradigm consisted of three different tasks: Control, Reward, and Novelty. During each task, the subjects were asked to passively look at a casino wheel spinning on a computer screen positioned approximately 1 m in front of their eyes (Fig. 1).

On each trial of the Control task, the wheel spun for 10 s and always started and ended on the same number, followed by a blank screen. In contrast, on each trial of the Reward and Novelty tasks, the wheel spun for a variable duration, and stopped on different numbers. In the Reward task, after the wheel stopped, the screen showed the amount of money earned on that trial, which was the number on which the wheel stopped multiplied by a multiplier that increased throughout the task. The subjects also heard a cash register sound. The subjects saw a running total of their earnings after each trial. If the wheel landed on an asterisk, a different sound occurred and the multiplier increased (e.g., if the multiplier were "1", then landing on 10 would lead to a reward of 10 cents; if the

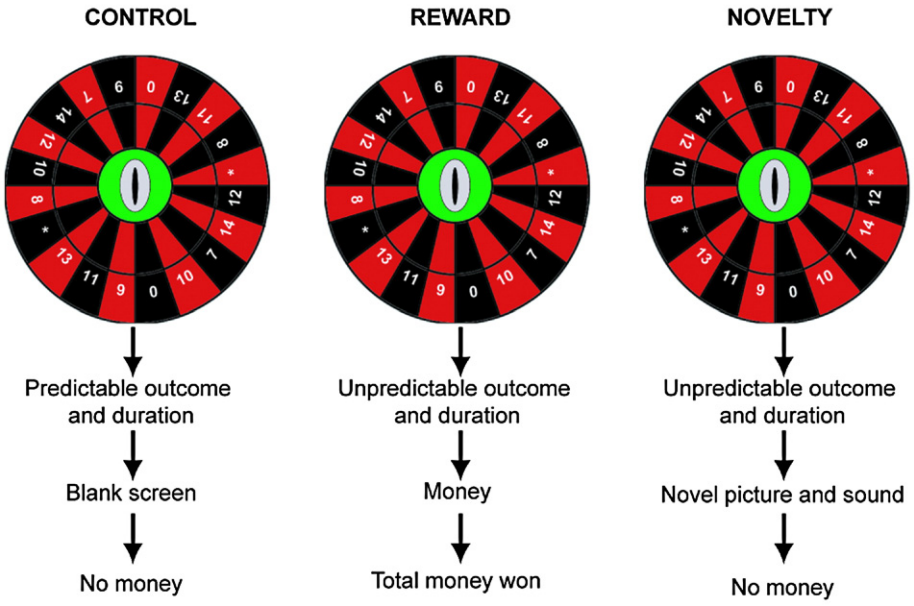

Fig. 1. Stimulation paradigm schematic representation of the stimulation task. On the 3 different tasks the subjects were passively looking at a casino wheel. In the Control condition, each spin of the wheel or trial lasted 10 s and always started and ended on the same number, followed by a blank screen, and no money was earned. In the Reward and the Novelty conditions, each trial had a different duration and the wheel stopped on a different number. In the Reward condition each trial was followed by monetary reward with a cash register sound, and the total amount of money earned; 9 times out of 10 the trials were rewarding. In the Novelty condition, each trial was followed by novel sound and image, but no money was earned.

multiplier were "5", then landing on the 10 would lead to a reward of 50 cents). Only on 10% of the trials did the subject not receive a monetary reward. Participants were informed that they had no power over the outcome of the game and that earnings would depend on how lucky they were. However, the task followed a pseudorandom schedule, such that all subjects earned $217 CDN.

In the Novel stimulation condition, participants did not receive a monetary reward. After the roulette wheel stopped spinning, the subjects saw a novel picture and heard a novel sound. Novel pictures consisted of photographs that were manipulated with Adobe Photoshop 7.0 (Adobe Systems Inc, San Jose, CA) to distort the shape and/or alter the color configurations of the images (see Fig. 2 for example). Novel sounds consisted of 1- to 2-s clips of nonaversive sound clips taken from Royet et al. (2000). Each sound was played only once. Many of these sounds are identifiable but are not heard on a daily basis, and in some cases were played in reverse to make them more unusual.

Mood and wanting measures

Mood was measured four times during each PET scan session using the Positive Affect Negative Affect Schedule (PANAS: Watson, 1988). Participants' level of desire to continue the task was also assessed with the question "how much do you want to pursue the task." Questions were asked at baseline, after 10 min of performance, after an additional 10 min of the task, and upon completion of the task.

[^{11}C]raclopride PET imaging and analysis

Before starting the stimulation paradigm, an example of the visual stimuli was presented on the computer screen. Because [^{11}C]raclopride binding is likely to be most sensitive to stimulation occurring immediately prior to and after injection, the tasks started approximately 15 min before [^{11}C]raclopride injection and terminated 15 min post-injection.

While performing the task, but prior to injection, subjects received a 10-min ^{68}Ga transmission scan for attenuation corrections. PET measurements were conducted using a Siemens HR+ tomograph, which produces 63 transverse planes at an intrinsic spatial resolution of 4.2-mm full width at half maximum (FWHM). Twenty-six emission frames of increasing length were collected over 60 min, beginning with radiotracer arrival in the brain.

Particular care was taken to limit the subjects' movement during the scans. To detect and correct potential movement-related errors, we employed an automated movement detection procedure designed by S. Sechet, A. Reilhac, R.N. Gunn, A. Evans and A. Dagher A (unpublished manuscript). The method uses the subject's MRI, which is segmented automatically into several user-determined regions, using the program ANIMAL (Collins et al., 1994). Each region is then assigned a generic [^{11}C]raclopride time–activity curve based on data collected on our ECAT HR+ camera in normal volunteers. Thus we generate a 4D data set, which is then filtered using the characteristics of the ECAT HR+. This PET template, which is generated for each subject, has the appropriate spatial and temporal characteristics to serve as a target for realignment. We then use this realignment algorithm to determine the amount of movement in every frame relative to this target volume. When the algorithm detects significant movement the realignment data are used to realign the subject's [^{11}C]raclopride data. PET images were coregistered to the MR images using automated methods. Voxelwise [^{11}C]raclopride BP was calculated to generate parametric images using the simplified reference model (Lammertsma et al., 1996;Gunn et al., 1997), with the cerebellum as the reference region. The reference region was drawn on 10 adjacent slices on each subject's MRI. For group voxelwise analyses, each MRI was linearly transferred into standard stereotaxic space (Collins et al., 1994), and this transformation algorithm was applied to the coregistered PET images.

Magnetic resonance imaging

Each subject underwent high-resolution MRI scanning for use in ROI definition and intersubject coregistration. All studies were carried out either at the Montreal Neurological Institute or at the Westmount Square Clinic (Montreal, Quebec), on a 1.5-T MR scanner. T1-weighted structural images were acquired with a TR=9.7 ms, TE=4 ms, flip angle=12°, FOV=250, and matrix 256×256.

Statistical analysis

DA transmission was indexed by changes in [^{11}C]raclopride BP across conditions. Statistical significance was assessed in two ways. Changes in DA transmission were first assessed using a statistical parametric map strategy (Aston et al., 2000). A statistical significance of $p=05$ corrected for multiple comparisons was utilized, with the threshold based on the methods of Worsley et al. (1996). This method corrects for multiple comparisons on the basis of the search volume and spatial resolution of the image. Because

Fig. 2. Examples of novel stimuli presented in the Novelty condition.

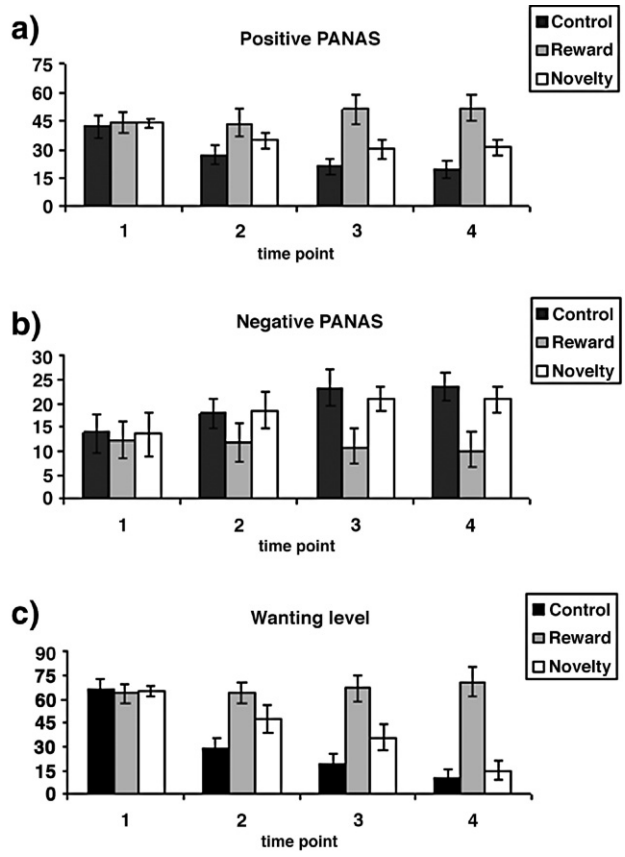

Fig. 3. Average positive (a) and negative (b) affect ratings of the PANAS, and wanting ratings (c) in the different conditions across the four time points of each condition (before, 10 min in, 20 min in and at the end of performing the task).

[^{11}C]raclopride only binds specifically within the striatum, the search volume in the striatum was defined as all the voxels with a mean BP > 1, averaged over all the scans. A spatial resolution of 12-mm full width at half maximum (FWHM) was used in the calculation of the number of resolution elements. This led to a significance threshold of $t = 3.85$.

In addition, BP values were extracted from each PET scan with regions of interest (ROIs) drawn on the subject's MRI over the caudate nucleus, putamen, and ventral striatum following the method described by Martinez et al. (2003). BP values extracted from the ROIs were analyzed using a three-way analysis of variance (ANOVA) for dependent samples (Condition × ROI × Hemisphere) followed with post hoc pairwise comparisons using the Tukey's honestly significant difference test when appropriate.

Results

Ten subjects out of twelve provided valid PET data. One subject was eliminated from the study because the post-scan debriefing revealed that he had misinterpreted the pre-scan instructions such that he did not believe there were any real rewards in the monetary reward tasks and therefore did not become positively engaged in the task. One subject was eliminated due to excessive head motion.

Mood data

Repeated measures ANOVA of positive affect with three conditions and four time points revealed a significant effect of condition ($F_{2,18} = 9.5$, $p < 0.005$) (Fig. 3a). There was also a significant effect of time ($F_{3,27} = 7.8$, $p = 0.001$) and a time × condition interaction ($F_{6,54} = 6.6$, $p < 0.001$), reflecting a decline in positive affect in the Control condition and, to a lesser extent, in the Novelty condition, while positive affect modestly increased over the same time span in the Reward condition. Repeated measures ANOVA of negative affect ratings also revealed an effect of condition ($F_{2,18} = 13.7$, $p < 0.001$) (Fig. 3b). There was also a significant effect of time ($F_{3,27} = 4.6$, $p = 0.01$) and a time × condition interaction ($F_{6,54} = 5.7$, $p < 0.001$), reflecting an increase in negative affect during the task for the Novelty and Control conditions, but not for the Reward condition.

Repeated measures ANOVA also revealed significant condition effects on wanting to pursue more trials ($F_{2,18} = 35.2$, $p < 0.001$). As with the other ratings there was a significant effect of time ($F_{3,27} = 21.1$, $p = 0.001$), and a significant condition × time interaction ($F_{6,54} = 15.6$, $p < 0.001$). As can be seen in Fig. 3c, this interaction reflected a strong decrease in the desire for more Novelty or Control trials, whereas desire for more monetary Reward trials remained robust even at the end of the task.

DA transmission

The Reward condition failed to induce any significant increases in DA transmission relative to the Control condition. Rather, the Reward condition produced a significant decrease in DA transmission in the left putamen relative to the Control condition. Fig. 4

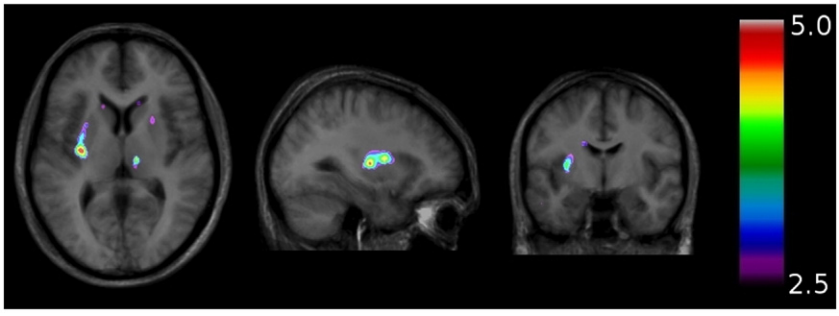

Fig. 4. Increased [^{11}C] raclopride BP (indicating decreased DA transmission) in the left dorsal putamen in the Reward versus Control conditions. The t statistic map was threshold to only show changes of $t > 2.5$ (positive t-values reflect increased [^{11}C] raclopride BP). In all images, the t statistic maps for BP change are overlaid on axial slices from an average MRI of the 10 subjects. Left and right on the images correspond to the real left and right sides.

Table 1
Peaks of significant changes in DA transmission

Location	Talairach coordinates	%BP change mean (SD)	*T* value	Vol. (mm^3)	*P* value
Reward − Control					
Left lateral putamen	−32 −12 6	14 (10)	4.96	1256	0.003
Right caudate	14 24 10	18 (23)	3.76	96	0.042
Left caudate	−14 20 12	11 (16)	3.68	88	0.053
Novelty − Control					
Right putamen	30 8 10	11 (11)	4.5	656	0.003

Peak coordinates of areas showing significant changes in DA transmission. Peaks of significant change were only detected in the Reward and Novelty conditions versus the Control task. A positive *t* value indicates greater [^{11}C]raclopride BP in the Reward and Novelty condition.

displays a *t*-map of this contrast, revealing a significant increase in BP in the left putamen (peak *t*-value of 4.96 and cluster size 1256 mm^3, $p<0.005$). There was a trend towards a decline in the caudate, but these fell just below statistical significance ($t=3.7$ and 3.8, in the left and right caudate respectively). Table 1 displays the peak coordinates, percent change, and *t*-value of change in [^{11}C]raclopride BP.

In previous work with amphetamine, Leyton et al. (2002) reported an association BETWEEN wanting (more amphetamine) and the amount of DA release. We therefore calculated the relationship between changes in ratings of wanting (more trials), between the Reward and the Control conditions, and changes in BP. A significant correlation emerged between ratings of wanting and BP change in the right caudate and putamen, such that the greater the increase in wanting, the greater the suppression of DA transmission ($r=0.83$ and 0.81, $p<0.01$; Fig. 5).

The Novelty condition also failed to produce increased DA transmission relative to the Control condition. Rather it produced a significant suppression of DA release in the right putamen (peak *t*-value of 4.65, 656 mm^3, $p<0.005$, Fig. 6). No differences emerged between the Reward and Novelty conditions.

Fig. 7 displays the results of region of interest (ROI) analyses. ROI analyses primarily provide an index of regionally broad changes in BP and therefore are unlikely to reach significance if changes are limited to only a portion of a given region. Not surprisingly, a three-way ANOVA with condition, region and hemisphere, failed to show any significant main effects or interactions (all $F<4.05$, $p>0.05$).

Discussion

In the present study, we failed to observe any significant increases in DA transmission during either a passive unpredictable monetary reward task or a passive novelty task. The absence of increased DA transmission during a reward on the surface appears inconsistent with a wealth of studies in animals in which DA release has been observed in the striatum upon exposure to salient stimuli such as food (Hernandez and Hoebel, 1988; Wilson et al., 1995), cues that signal the availability of food reward (Schultz, 1998), or novelty (Legault and Wise, 2001; Horvitz, 2000). It is also inconsistent with several previous [^{11}C]raclopride studies in humans which have observed increases in DA release in response to tasks such as playing a video game (Koepp et al., 1998), exposure to highly palatable food (Small et al., 2003), and exposure to drug cues in drug-dependent subjects (Volkow et al., 2006). Importantly, in our previous study with monetary reward, we had observed a significant increase in DA transmission in the caudate during unpredictable reward (Zald et al., 2004). This DA release had occurred despite the use of a lower ratio of reward to nonreward in the earlier study compared to the current one.

However, unlike our past research, the present study was entirely passive in nature. Subjects did not have to make any movement or make any decisions during the task. This contrasts with many of the previous reward-related [^{11}C]raclopride studies in which operant or consummatory movements were performed. In microdialysis studies, the amount of DA release is often associated with the amount of work that the animal has to perform to obtain the reward (Sokolowski et al., 1998). Indeed, Salamone et al. (1994) have reported that DA release increases when animals have to work for food, but not when the food is given freely. Similarly, depletions of DA (preventing appropriate DA release) impair the readiness to work for food, rather than the readiness to consume food (Cousins et al., 1996; Aberman and Salamone, 1999).

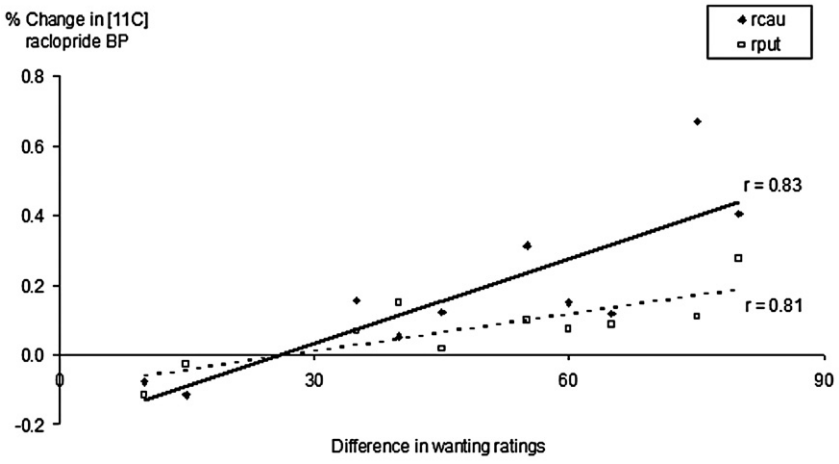

Fig. 5. Correlation between the percent change in [^{11}C] raclopride binding potential in the Reward–Control contrast and the wanting ratings. The *x*-axis displays the subjective rating of wanting at time point 3 during the task, and the *y*-axis shows the percent change in [^{11}C] raclopride between conditions. Separate fit lines are shown for the right caudate (rcau) and the right putamen (rput).

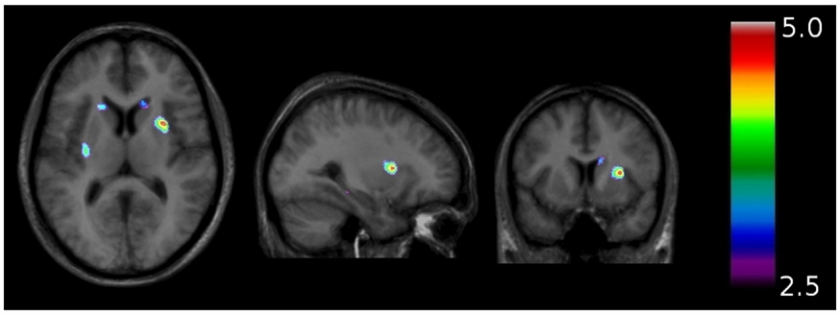

Fig. 6. Increased [^{11}C] raclopride BP (indicating decreased DA transmission) in the right anterior putamen in the contrast Novelty versus Control conditions. The *t* statistic map was threshold to only show changes of $t > 2.5$ (positive *t*-values reflect increased [^{11}C] raclopride BP).

Multiple fMRI studies have found that striatal responses to reward are often contingent upon the need to make a motor response (Elliott et al., 2004; Bjork and Hommer, 2007). Indeed, in one experiment Zink et al. (2004) reported that passively received monetary reward caused overall less striatal activation than passively viewed nonrewarding stimuli. Taken in this light, the present data support the existing literature on the importance of behavioral demands on DA responses in the striatum. Future studies assessing DA transmission during reward in humans may be best carried out in the context of tasks that require subjects' active involvement in making instrumental responses or decisions.

The present results do not necessarily run counter to models which emphasize that DA cells fire phasically in response to unpredictable rewards (Schultz, 2001). The precise aspect of unpredictability varies somewhat between the animal literature and the present paradigm. In animal studies, the presence of the reward itself is unpredictable or unanticipated. In contrast, in the present study participants knew that the receipt of some reward was likely on most trials. Rather, the timing and the size of the reward were primarily unpredictable. However, our manipulation is easily comparable to past fMRI studies that have capitalized on temporal unpredictability and interpreted their results in terms of phasic DA signals. For instance, Berns et al. (2001) observed a BOLD fMRI response in the ventral striatum during receipt of unpredictably timed and sequenced oral delivery of juice and water relative to predictably timed and sequenced stimulations. Similarly, using a passive conditioning task and BOLD fMRI, McClure et al. (2003) demonstrated that delivery of juice reward at a later than expected time produced changes in BOLD signal in the left dorsal striatum.

Unfortunately, the timing limitations of the [^{11}C]raclopride technique make it difficult to construct a [^{11}C]raclopride study that specifically examines breaches from reward expectations. Whereas event-related fMRI studies are capable of capturing blood oxygenation changes in the striatum on individual trials in which reward expectations vary (for example, see Spicer et al., 2007), [^{11}C]raclopride studies of DA transmission require integration of data over an extended period of time. Indeed, this longer timescale for [^{11}C]raclopride studies must be considered when contrasting this work with electrophysiological studies in animals that capture phasic burst firing at the millisecond level.

Because of its slower timescale, changes in [^{11}C]raclopride BP reflect a net change in DA transmission including both mean levels of phasic responses and any more sustained statewise changes in tonic firing. Such net statewise changes may be related to different aspects of behavior than specific phasic firing bursts. For instance, statewise or net changes in extrastriatal DA levels often appear dependent upon motor effort (McCullough et al., 1993; Sokolowski et al., 1998; Salamone et al., 1994), whereas phasic firing shows

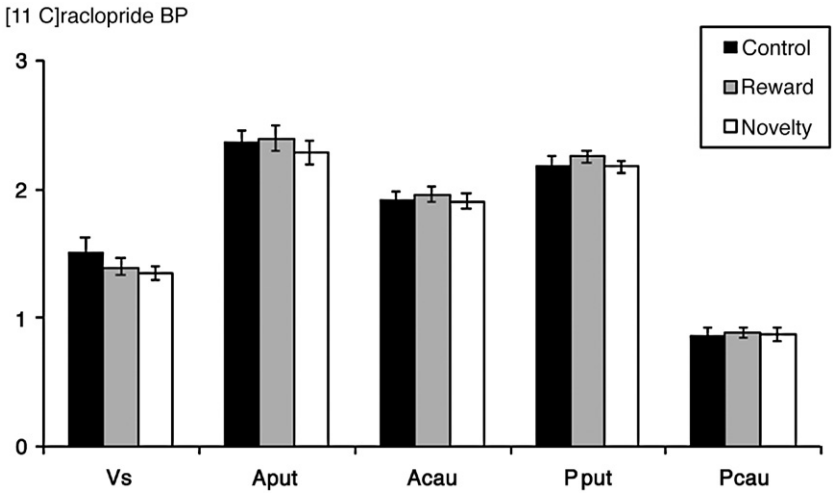

Fig. 7. Average [^{11}C] raclopride BP in the regions of interest. BP in the three conditions are shown for the ventral striatum (Vs), anterior putamen (Aput), anterior caudate (Acau), Posterior putamen (Pput), and posterior caudate (Pcau).

little association with individual motor responses per se (DeLong et al., 1983; Schultz and Romo, 1990; Schultz et al., 1983).

It is also possible that the sensitivity of the [^{11}C]raclopride technique is too low to detect a change in a passive paradigm, except when there is an extreme salience, such as with drug cues (Volkow et al., 2006), or an additional pharmacological manipulation (Volkow et al., 2002). Studies with combined microdialysis and [^{11}C]raclopride measurement indicate that increases in DA transmission as measured with [^{11}C]raclopride are many fold lower than the amount of change observed with microdialysis (Breier et al., 1997). However, the present results were not totally devoid of significant changes in [^{11}C]raclopride BP. Rather, changes were observed in the parametric maps but showed decreased DA transmission rather than increased transmission. In our original study (Zald et al., 2004) we suggested that observations of decreased DA transmission might reflect the high frequency of nonrewarded trials, which should be associated with suppressed phasic DA firing, but that is unlikely to explain the present results, since only 10% of trials were not rewarded. The source of these areas of decreased DA transmission is unclear, but we have now observed them in two studies of monetary reward and one study of novelty. The consistency of their emergence suggests that they are not simply due to random noise but rather reflect a real response to the stimulation paradigms.

The suppression is particularly surprising in light of theoretical models stressing relationships between DA and wanting (Berridge, 1996). The Reward condition induced substantially more sustained positive affect and desire for more trials than the control condition but resulted in a decrease in DA release in the striatum. Moreover, the degree of suppression appeared related to task engagement as indexed by ratings of how much subjects wanted more trials.

Why would DA decrease in the putamen? One intriguing possibility is that statewise tonic changes might occur that appear in opposition to phasic firing. If tonic and phasic DA oppose one another (Grace, 1991), the focal signal conveyed by phasic DA burst firing could be accentuated under conditions of low tonic DA. Such a dissociation between phasic burst firing and more statewise tonic DA activity is consistent with evidence of dissociable influences on DA cell firing and release. Cortical inputs onto presynaptic dopamine terminals and pallidal afferents that selectively modulate the population activity of DA neurons are capable of producing long-lasting modulations of extrasynaptic striatal DA levels, whereas afferents from the pedunculopontine tegmental nucleus selectively modulate phasic burst firing (Floresco et al., 2003). Thus it is possible to selectively modulate the tonic level of DA firing, providing an altered context for the response to phasic firing. Within this model, areas with phasic increases and tonic decreases might not display a change in [^{11}C]raclopride binding (because the net effects would cancel out over the course of scan), while areas lacking phasic increases would show a net reduction in DA release due to the global tonic decrease. However, such a hypothesis is highly speculative. The relative effects of phasic and tonic DA release on the raclopride signal are not known, and indeed the frequently focal nature of changes is probably more consistent with phasic effects. As in past behavioral studies, the areas showing significant declines in DA release were quite focal and indeed were often lateralized (predominantly left in the Reward condition, and right in the Novelty condition). Some of this focal appearance is an artefact of the strict statistical thresholding. But even with less thresholding it is clear that the changes do not reflect a global modulation of DA transmission. In our previous reward study (Zald et al., 2004), which required active right hand button pressing, we speculated that the lateralization of effects related to lateralized motor demands. However, the present results cannot be explained by motor demands since the tasks were totally passive in nature. Other factors related to functional asymmetries in the cortical regions projecting to the striatum may explain these patterns. Interestingly, in McClure et al.'s (2003) study of passive conditioning with temporal deviations in reward delivery time, responses to temporal deviations localized to the left putamen. A right localization for the Novelty condition would also be consistent with the greater right hemisphere involvement in processing novel stimuli (Goldberg and Costa, 1981). Thus, the pattern of lateralized responses appears consistent with other literature. However, in the absence of a fuller understanding of the mechanisms underlying the observed declines in DA transmission, a comprehensive explanation of the observed pattern of declines in DA transmission within the putamen remains elusive.

Acknowledgments

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