Striatal dopamine release during performance of executive functions: A [¹¹C] raclopride PET study

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Abstract

To date, while the contribution of the striatum in executive processes is well documented, the role played by striatal dopamine during tasks requiring executive functions is still unknown. We used D2-dopamine receptor ligand [¹¹C] raclopride PET in healthy subjects while performing the Montreal Card Sorting Task (MCST). We observed a striatal reduction in [¹¹C] raclopride binding potential during planning of a set-shift when compared with matching according to an ongoing rule. These findings suggest that striatal dopamine neurotransmission increases significantly during the performance of specific executive processes confirming previous evidence of striatal activation during fMRI studies. The present observation may provide some insights on the origin of cognitive deficits underlying certain neurological disorders associated with dopamine dysfunction, such as Parkinson's disease.

Keywords

Positron emission tomography; Functional imaging; Raclopride; Dopamine; Basal ganglia; Executive functions; Cognition

Introduction

Functional neuroimaging studies have shown the involvement of the striatum and the caudate nucleus in particular in executive processes requiring planning and set-shifting (Lewis et al., 2004; Monchi et al., 2001, 2006; Owen, 2004; Rogers et al., 2000). Recently, we developed a new task, the Montreal Card Sorting Task (MCST), to study the specific role of the striatum in executive processes (Monchi et al., 2006). Using functional magnetic resonance imaging (fMRI), we demonstrated that, while both the caudate nucleus and putamen are specifically engaged in conditions where planning is required to perform a set-shift, neither of them are activated when the rule for shifting is implicitly given by the task. Based on these results, we proposed that the caudate nucleus is involved in the planning while the putamen plays a role in the execution of a self-generated novel action (Monchi et al., 2006).

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To date, while the contribution of the striatum in executive processes is well documented, the role played by striatal dopamine during the performance of tasks requiring executive functions is still unknown. Previous studies of dopamine depletion in non-human primates have proposed a possible involvement of striatal dopamine in set-shifting tasks (Collins et al., 2000; Roberts et al., 1994). In humans, striatal dopamine is involved in a wide range of motor functions (Goerendt et al., 2003; Ouchi et al., 2002) and reward processes (Zald et al., 2004) but its release during tasks involving executive functions such as planning and set-shifting has yet to be demonstrated. Some neuroimaging studies have proposed that changes in striatal dopamine levels can modulate certain cognitive processes and that level of cognitive impairment may be dependent on the level of dopamine depletion (Crompton et al., 2006). Consistent with this hypothesis, positron emission tomography (PET) studies performed both in healthy subjects (Mehta et al., 2005), following tyrosine and phenylalanine-induced depletion, and patients with Parkinson's disease (PD) (Marie et al., 1999; Lozza et al., 2004) have shown significant correlation between executive task performances and striatal dopamine denervation.

Confirming an involvement of the dopaminergic system in these cognitive processes would be important for understanding the neural bases of functions such as planning and set-shifting and as well as for revealing the neurochemical substrate underlying deficits in cognitive functions observed in neurological disorders associated with dopamine dysfunction, such as PD. In this condition, deficits of executive functions are well documented even at early stage of the disease (Monchi et al., 2004; Owen, 2004; Taylor and Saint-Cyr, 1995) and appear to be extremely sensitive to the effects of controlled L-dopa withdrawal (Lange et al., 1992; Lewis et al., 2005).

In order to investigate the contribution of striatal dopamine during set-shifting, we tested young healthy subjects with PET during retrieval with and without shift conditions of the MCST. During this card sorting task, the subject has to match a test card to one of four reference cards by comparing the test card to a previously shown cue card held in memory in order to find the rule for classification (Fig. 1). We used D2-dopamine receptor ligand [^{11}C] raclopride which binding has been shown to be inversely proportional to the concentration of extracellular dopamine (Endres et al., 1997; Laruelle, 2000). In humans, this method has been used to measure striatal dopamine release in response to drugs (Dewey et al., 1993; Laruelle et al., 1997), behavioral tasks (Koepp et al., 1998) and repetitive transcranial magnetic stimulation (Strafella et al., 2001, 2003, 2005). We predicted that those trials of the MCST where planning a set-shift was required would lead to a reduction in raclopride binding (indicating release of dopamine) in the striatum compared to those conditions where the same rule for classification was requested.

Methods

Experimental design

Six healthy subjects (20–33 years, 2 males and 4 females) participated in the study after having given written informed consent. Each subject underwent two [^{11}C] raclopride PET scans at the same time on two different days while performing the MCST (Fig. 1). A [^{11}C] raclopride PET was obtained during performance of the retrieval with shift condition and a

control scan during performance of the retrieval without shift condition. The scan order was counterbalanced across subjects. The experiments were approved by the Research Ethics Committee of the Montreal Neurological Institute and Hospital.

Positron emission tomography

PET scans were obtained with a CTI/Siemens HR plus tomograph operating in 3-D mode, yielding images of resolution 4.2 mm full width at half maximum (FWHM). 10 mCi of [^{11}C] raclopride was injected into the left antecubital vein over 60 s, and emission data were then acquired over a period of 60 min in 26 frames of progressively increasing duration. After the emission scan, a 10-minute transmission scan was performed with a rotating radioactive source (^{68}Ga) for attenuation correction.

A high-resolution MRI (Siemens Sonata 1.5 T; T1-weighted images, 1 mm slice thickness) of each subject's brain was acquired and transformed into standardized stereotaxic space (Talairach and Tournoux, 1988) using automated feature-matching to the MNI template.

PET frames were summed, registered to the corresponding MRI and transformed into standardized stereotaxic space using the transformation parameters previously determined for the MRI. Voxelwise [^{11}C] raclopride binding potential (BP) was calculated using a simplified reference tissue (cerebellum) method (Gunn et al., 1997; Lammertsma and Hume, 1996) to generate statistical parametric images of change in BP (Aston et al., 2000). Only those peaks falling within the striatum were considered. A reduction in [^{11}C] raclopride BP is indicative of an increase in extra-cellular dopamine concentration. A threshold level of t 4.1 was considered significant ($p < 0.05$, 2-tailed) corrected for multiple comparisons (Worsley et al., 1996), assuming a search volume equal to the entire striatum, an effective image filter of 6 mm FWHM and 276 degrees of freedom (Aston et al., 2000). Binding potential values were extracted from a spherical region of interest (radius 5 mm) centered at the x , y and z coordinates of the statistical peak revealed by the parametric map. Coordinates listed below are expressed in Talairach space.

Cognitive task

We used two conditions of the MCST (Monchi et al., 2006). In the MCST, four reference cards were on display in a row at the top of a computer screen in all trials. On each classification trial, a new test card was presented below the reference cards and the subject had to match the test card to one of the four reference cards using one of four buttons with the right hand. The match of each test card to one of the reference cards was determined by a classification rule (color, shape or number) that is determined by making a comparison between a previously cued card and the current test card. There were two different experimental conditions: (1) retrieval with shift (Figs. 1D–E) and (2) retrieval without shift (control condition, Figs. 1B–C). In both conditions, a series of classification trials were preceded by the brief presentation of a single cue card (Fig. 1A). This was then followed by a blank period. The cue card did not reappear and had to be remembered throughout the series of classification trials. For every trial, a new test card that shared a single attribute with the cue card held in memory was presented beneath the reference cards (Figs. 1B–E). The subject was asked to select one of the four reference cards based on this attribute.

In both conditions, a block was comprised of 20 trials. A different cue card was presented before each block for both conditions. In the retrieval with shift condition, the test cards on consecutive trials never shared the same attribute with the cue card. Therefore, matching had to be performed according to a different attribute for each trial (Figs. 1D–E). In the retrieval without shift condition (Figs. 1B–C), all the test cards shared the same attribute with the cue card meaning that matching had to be performed according to the same classification rule for each trial. Several blocks of a single condition were repeated on a given scanning session. A rest period of 1 min was given between all 5-minute testing period. For each scan, the subject performed two five-minute blocks prior to the injection and eight 5-minute periods after the injection. Subjects underwent a brief training session consisting of five 20 trial blocks before the first PET session in order to familiarize themselves with the tasks. In addition, no incentives (financial reward or other) were provided or suggested to the subjects for the accuracy of their performance, thus no reward component was present in the task.

Results

The retrieval with shift condition of the MCST induced a bilateral reduction in [^{11}C] raclopride BP in the dorsal striatum as compared to the control (retrieval without shift) condition (Figs. 2 and 3). The retrieval with shift condition induced a 10.2% decrease in [^{11}C] raclopride BP in the left caudate nucleus compared to control condition (mean $\pm$ SD, control condition: 2.654 ± 0.37 , active condition: 2.383 ± 0.28 , paired t test $p=0.03$). The area with decreased [^{11}C] raclopride BP had its peak ($t=4.1$, cluster size: 83 voxels, 670 mm^3) at coordinates $x=-14$, $y=12$, $z=14$, extending from $z=12$ to 16 (Figs. 2 and 3). This reduction in binding was in the order of 9.1% (mean $\pm$ SD, control condition: 2.647 ± 0.36 , active condition: 2.405 ± 0.24 , paired t test $p=0.04$) in the contralateral caudate nucleus ($t=4.1$, cluster size: 42 voxels, 336 mm^3). Another significant area of change in [^{11}C] raclopride binding was also observed in the right anterior putamen, 13.8% (mean $\pm$ SD, control condition: 2.503 ± 0.33 , active condition: 2.156 ± 0.20 , paired t test $p=0.01$) (Figs. 2 and 3), with its peak ($t=4.3$; cluster size: 94 voxels, 752 mm^3) at coordinates $x=23$, $y=5$, $z=12$, extending from $z=9$ to 15 . No significant changes in BP were detected in the ventral part of the striatum (Fig. 2). No reduction in BP was found anywhere in the striatum with the reverse subtraction (i.e., when comparing the control, retrieval without shift, vs. the retrieval with shift condition). There was no difference in task performance; subjects performed with a mean accuracy of 97.29% in the retrieval with shift condition and 99.79% in the retrieval without shift (control) condition. Thus, striatal dopamine release could not be the consequence of poor performance or different error rate between the two conditions.

Discussion

The present results confirm previous observations that the striatum plays a key role in the cognitive planning of a novel action and that the dopaminergic system seems to be involved in this process. To our knowledge, this is the first study showing that striatal dopamine neurotransmission increases significantly during the performance of executive processes. Specifically, striatal dopamine is released during planning of a set-shift (compared with matching according to an ongoing rule). However, we would like to point out that, since the retrieval with shift condition involved a more demanding cognitive processing than the

control task, we cannot rule out that other cognitive features of the task, beyond planning and set-shifting, may have played a certain role in modulating the release of dopamine in the striatum. Indeed, while the retrieval with shift condition required that all the features of the cue card (i.e., color, shape, and number) would be stored in short term memory, in the retrieval without shift condition, only one feature needed to be remembered.

These findings of striatal dopamine release during set-shift tasks are consistent with previous studies of dopamine depletion in non-human primates which reported a possible involvement of striatal dopamine in set-shifting tasks (Collins et al., 2000; Roberts et al., 1994). Similarly, indirect observations in PD have shown that controlled L-dopa withdrawal resulted in decreased executive functions (Lange et al., 1992; Lewis et al., 2005), thus implying a potential role of the dopaminergic substrate for the deficits observed.

Changes in BP were observed in the dorsal part of the caudate nuclei and anterior putamen (Fig. 2). These findings are in accordance both with anatomical and functional imaging studies. Indeed, studies in rhesus monkeys have shown that both these striatal areas receive axonal afferents mainly from the prefrontal cortex and form part of the 'cognitive' corticostriatal loop proposed by Alexander et al. (1986). Similarly, in our recent fMRI studies, we have reported a co-activation of the ventrolateral and the posterior prefrontal cortex with the caudate nucleus and putamen, respectively, during planning and execution of a set-shift (Monchi et al., 2001, 2006). Thus, we proposed that the caudate nucleus and putamen are likely to play a critical role in the cognitive planning and execution of a self-generated novel action, respectively (Monchi et al., 2006). It is worth noting that the putamen, unlike the caudate nucleus, has traditionally been associated more with motor-related activities rather than cognitive functions. However, there has been evidence that the role of the putamen may not be directly linked to the movement itself, but rather to the condition under which it is made (Tolkunov et al., 1998).

The activation of both the caudate nucleus and putamen observed in our previous event-related fMRI study of the MCST when comparing the retrieval with shift to the retrieval without shift condition (Monchi et al., 2006) and the striatal dopamine release measured with [^{11}C] raclopride PET, in the same context of set-shifting and planning, appear to suggest a possible link. However, it should be noted that, unlike our event-related fMRI studies (Monchi et al., 2001, 2004, 2006), the block design of [^{11}C] raclopride PET does not allow us to separate out the different stages and components of the set-shifting task contributing to striatal dopamine release.

The lack of dopamine release in the ventral part of striatum (Fig. 2) was consistent with the fact that the task did not contain a reward or penalty component.

The present study does not provide any insight into the relationship between hemispheric laterality and cognitive functions. Previous neuroimaging studies investigating cognitive processes have also provided controversial findings. Indeed, while some fMRI experiments in healthy subjects have reported an activation of only the right caudate nucleus (Huettel et al., 2002; Monchi et al., 2006; Rao et al., 1997), other studies have shown a bilateral caudate activation (Lewis et al., 2004; Monchi et al., 2001). In addition, PET studies in PD have

demonstrated only a unilateral striatal involvement with significant correlation between the right caudate nucleus and frontal executive tasks (Bruck et al., 2001; Marie et al., 1999). These discrepancies, however, are not surprising considering the different parameters measured (e.g. activation, binding potentials, uptake etc.) and study designs (e.g. block, event related, etc.).

Even though the release of dopamine was consistent across all subjects (Fig. 3), the limited number of participants imposes us to be cautious in generalizing this observation and extending our findings to all executive processes.

The present study supports the role of dopaminergic neurotransmission in set-shifting tasks; however, this observation does not rule out the possible contribution of other neuronal networks. In fact, recently, Aalto et al. (2005), studying *cortical dopamine release* in healthy individuals using [^{11} C]FLB 457 PET, reported decreased binding in the ventrolateral prefrontal cortex and medial temporal cortex during the performance of conditions with similar cognitive requirements as in the MCST such as tracking and retention of events in working memory, but not requiring set-shifting. These observations are in line with later reports proposing that changes in dopamine levels can modulate certain cognitive processes (see review by Cropley et al., 2006). However, cholinergic and noradrenergic pathways seem also to play an important role in cognitive functioning (Dubois et al., 1983; Scatton et al., 1983).

The finding of spatially restricted dopamine release has implications for models of basal ganglia function. One of these models proposes that, during a task, there is specific enhancement of activity in corticostriatal loops involved in the current task with concomitant suppression of competing motor networks (Mink, 1996). The neuroanatomical arrangement of the corticostriatal system in a center-surround inhibitory pattern is thought to facilitate this focusing function (Parent and Hazrati, 1993) and dopamine may play a significant role in this context (Wickens and Kotter, 1995). There is evidence that dopamine modulates corticostriatal activity by enhancing transmission at active synapses while suppressing it at inactive ones (Wickens and Kotter, 1995). Therefore, the effect of dopamine release in the vicinity of highly active corticostriatal terminations could be to increase the signal-to-noise ratio by strengthening that synapse while suppressing neighboring ones.

Our study provides preliminary evidence of an increase in dopamine neurotransmission during the performance of set-shifting processes; this may have potential implications for executive function deficits underlying certain neurological disorders associated with dopamine dysfunction, such as PD.

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Fig. 1.

Montreal Card Sorting Task. (A) An example of the cue card that appears for 3.5 s at the beginning of a block of retrieval trials. In this example, the cue card contains two red circles. The cue card changes for each block. (B, C) An example of two consecutive trials in the retrieval without shift condition. In B, since the color red is the only attribute shared by the test card and the cue, matching must be based on color. In the following trial (C) the test card is red and the matching is performed according to the same rule. This is the case for all subsequent trials within the same block. In this and the other examples, the orange line under one of the reference cards indicates the selected response. (D, E) An example of two consecutive trials in the retrieval trials with shift condition. (D) The test card contains four red stars and hence shares the color attribute with the cue card (containing two red circles, shown in A). (E) On the subsequent trial, the test card now shares a different attribute with the cue card (in this example “number”). Thus, a shift in classification category occurs requiring a novel response and such a shift is required for each subsequent trial.

Fig. 2.

Axial ($z=16$) and coronal ($y=10$) sections of the statistical parametric map of the change in [^{11}C] raclopride BP overlaid upon the average MRI of all subjects in stereotaxic space. The figure displays the significant areas of striatal dopamine release during the retrieval with shift condition compared to retrieval without shift condition (control): (a) left caudate: $t=4.1$ cluster size: 83 voxels, 670 mm³, (b) right caudate: $t=4.1$ cluster size: 42 voxels, 336 mm³, (c) right putamen: $t=4.3$ cluster size: 94 voxels, 752 mm³.

Fig. 3.

Individual $[^{11}\text{C}]$ raclopride binding potentials for each subject during retrieval with shift condition and retrieval without shift condition (control), from the left caudate ($p=0.03$) and right putamen ($p=0.01$), extracted from a spherical region of interest (radius 5 mm) centered at the x , y , and z coordinates of the statistical peak revealed by the parametric map.