

# Striatal dopamine release during unrewarded motor task in human volunteers

Rajendra D. Badgaiyan,<sup>1,2,CA</sup> Alan J. Fischman<sup>1</sup> and Nathaniel M. Alpert<sup>1</sup>

<sup>1</sup>Division of Nuclear Medicine, Massachusetts General Hospital and; <sup>2</sup>Department of Psychiatry, Harvard Medical School, Boston, MA 02114, USA

<sup>CA,1</sup>Corresponding Author: rajendra@wjh.harvard.edu

Received 3 March 2003; accepted 7 March 2003

DOI: 10.1097/01.wnr.0000080021.91618.ee

Striatal dopamine is associated with the processing of rewarded motor tasks. Its involvement in mediating unrewarded tasks is, however, unclear. We used a recently developed PET technique to dynamically measure the rate of displacement of a dopamine receptor ligand raclopride in healthy volunteers performing a finger opposition task. Rapid displacement of the ligand from the posterior putamen and the caudate immediately after the task initiation

suggested striatal dopamine release during task performance. Since dopamine release was observed in the striatal areas that are implicated in unrewarded tasks by neuroimaging studies, the results demonstrate that the PET method can be used to extend the findings of conventional neuroimaging techniques, that do not provide information about signal transduction. *NeuroReport* 14:1421–1424 © 2003 Lippincott Williams & Wilkins.

**Key words:** Alternative neuroimaging; Basal ganglia; Caudate; Dopamine; Neuroimaging; Neurotransmitter release; Putamen; Raclopride; Striatum; Unrewarded motor task

## INTRODUCTION

In recent years the roles of the basal ganglia and dopaminergic system in motor control have been studied extensively (for a recent review see [1]). Neuroimaging experiments have identified specific basal ganglia structures that are associated with different aspects of motor activity. These studies have found increased activation in the contralateral striatum during self-paced movements of a single finger [2], and also during rotation of joysticks in a freely chosen direction [3]. Generally, the activations are observed unilaterally when only one finger or arm is moved, and bilaterally when the task involves movement of more than one finger [4]. It has further been observed that during learning of a motor sequence the caudate is activated, while both caudate and putamen are activated during performance of prelearned motor movements [5]. These findings lend support to the hypothesis that the putamen mediates performance of learned patterns of movement while the caudate is more important for learning of new sequences [5].

To examine the role of the dopaminergic system in motor tasks, similar experiments were performed in patients with Parkinson's disease (PD). These experiments have reported longer response time and attenuated activation in the putamen when PD patients make self-paced movements of the fingers [2], or move a joystick in the freely chosen direction [3]. It has also been observed that, unlike healthy volunteers, these patients do not show basal ganglia activation during imagined motor movements [6]. These

findings have been interpreted to indicate that the dopaminergic mechanisms are involved in the motor tasks, and that its depletion results in attenuated activation of the basal ganglia and impaired task performance (for discussion see [1]). This interpretation is controversial, however, because it is known that dopamine deficiency does not account for all of the deficits in PD. Since these patients also have significantly altered cholinergic activities [7], many of the deficits in PD have been attributed to this alteration [7]. Cholinergic neurons also regulate various aspects of basal ganglia activity [8]. Thus, the findings of increased striatal activation and the demonstration of attenuated striatal activities in the PD patients do not necessarily indicate that the dopaminergic system is involved in the task performances.

Striatal dopamine has generally been associated with the reward system (for recent review see [9]). Dopamine burst firing during unpredictable reward has been observed in laboratory animals by many investigators [9], and a corresponding reduction of striatal raclopride (a dopamine receptor ligand) binding during performance of a gambling task [10], and during a rewarded video game [11] has been reported in human volunteers. These findings have prompted some investigators to suggest that the striatal dopamine is associated only with the motor tasks that are rewarded [9,12]. This suggestion has been supported by the neuroimaging studies that have shown increased activation of the striatum during presentation of rewarding stimuli [12]. These studies have further shown that the

reward-related activations are not found in the PD patients [12], providing additional evidence in support of the hypothesis that the striatal dopaminergic system regulates only the reward based motor tasks. This hypothesis, however, does not explain why increased striatal activation is observed in a number of unrewarded motor tasks [4,13].

The involvement of striatal dopaminergic system in the processing of unrewarded motor tasks is suggested by a recent experiment in which significant reductions in raclopride binding potentials (estimated using Logan plot) were found in the dorsal putamen during unrewarded foot extension/flexion movements [14]. Its involvement would however, be better understood if the release of dopamine could be demonstrated during an unrewarded motor task in healthy volunteers. Earlier studies from our laboratory suggested that the PET neuroimaging technique can be used to detect striatal dopamine released during a task performance [15,16]. Using this approach, dopamine release has been demonstrated in healthy human volunteers in a goal-directed motor task [11] and a gambling task [10]. Both of these experiments, however, used tasks that employed rewarding stimuli and a complex set of cognitive and motor activities. It is therefore still unclear from these studies whether striatal dopamine is involved in the processing of unrewarded motor tasks. We have recently modified this PET technique to make it more sensitive by using a newly developed kinetic model [17]. In the present experiment, using this dynamic PET neuroimaging technique, we have probed striatal dopamine release during a finger opposition task to examine whether the striatal dopaminergic system is involved in the processing of unrewarded motor tasks.

## MATERIALS AND METHODS

Six healthy right-handed young adult volunteers (mean age 21 years; two male, four female) participated in the study. None had a current or prior history of a neurological or psychiatric condition and none was taking any prescription or recreational drug. They were alcohol free for  $\geq 24$  h prior to the experiment and did not use tobacco for  $\geq 3$  h prior to the scan. After volunteers had signed the consent form approved by the IRB of the Massachusetts General Hospital, they were placed on the scanner bed and a single i.v. bolus of 6–14 mCi (sp. act. 700–1400 mCi/ $\mu$ mol) of a radiolabeled dopamine  $D_2$  receptor antagonist [ $^{11}$ C]raclopride was administered through the left antecubital vein over a period of 60 s. At the same time, the PET camera and a control task were started. In the control task a numeral, 1, 2, 3, or 4, was shown randomly for 1500 ms every 2 s on a computer monitor. The stimuli were presented in blocks of 2 min and a break of 15 s was allowed between the blocks.

Depending on the protocol, a finger opposition task was initiated at 25 or 38 min after the injection in different experiments. The task was initiated at different times to ensure that the effect was associated specifically with the task performance, and was not a non-specific change at a specific time point. Since the simulation [17] predicted that the activation could be detected best between 25 and 40 min of ligand injection, the tasks were initiated either at 25 or 38 min. In the initial experiments, tasks were initiated at 38 min and continued for 25 min. However, when we observed that the effects were significantly attenuated after

about 10 min, we decided to add another task block (in which fingers were remapped) to see whether a second activation could be obtained. In these experiments two tasks were initiated at 25 and 38 min. This strategy allowed us to demonstrate that a change in task initiation time caused the observed response to change appropriately. The core element of the motor task used was the opposition of the thumb and fingers of right hand in response to the visual cues presented on a computer monitor. The visual cues were the same as those shown in the control task (random presentation of a numeral once every 2 s). Subjects were instructed to oppose their right thumb and forefinger upon seeing the digit 1, their thumb and middle finger on seeing the digit 2 and so on. Three volunteers performed this task (single activation task) for about 30 min. In the remaining three experiments, the forward, i.e. 1, 2, 3, 4; and reverse, i.e. 4, 3, 2, 1 orders of finger opposition (multi-activation task) were used in 10 min alternating epochs.

PET data were acquired (using an ECAT EXACT HR + tomograph operating in 3D mode) at 30 s epochs in the first 5 min and then in 60 s epochs until the end of the experiment. Data were analyzed using a new analytical method [17], which is an extension of the simplified reference region model that accounts for the changes in kinetics from ligand displacement, and for the confounding effects of rCBF changes. This method employs weighted linear least-squares fitting on a voxel-by-voxel basis to estimate four parameters describing the transport and binding of [ $^{11}$ C]raclopride, as well as the time-dependent effects elicited by the task. The model of the instantaneous concentration history has the form:

$$\text{PET}(t) = R \cdot C_R(t) + k_2 \int_0^t C_R(u) du - k_{2a} \int_0^t \text{PET}(u) du - \gamma \int_0^t v(u-T) e^{-\tau(u-T)} \text{PET}(u) du$$

where  $C_R$  is the concentration in a region devoid of specific binding (reference), PET is the concentration in a voxel with specific binding, R is the ratio of transport rates for the binding and reference regions,  $k_2$  describes the clearance of nonspecifically bound tracer from the voxel,  $k_{2a}$  includes the information about dissociation from the receptor,  $\gamma$  represents the amplitude of transient effects,  $\tau$  is the rate at which transient effects return to baseline,  $t$  denotes the measurement time, T is the task initiation time and  $v(u-T)$  is the unit step function.

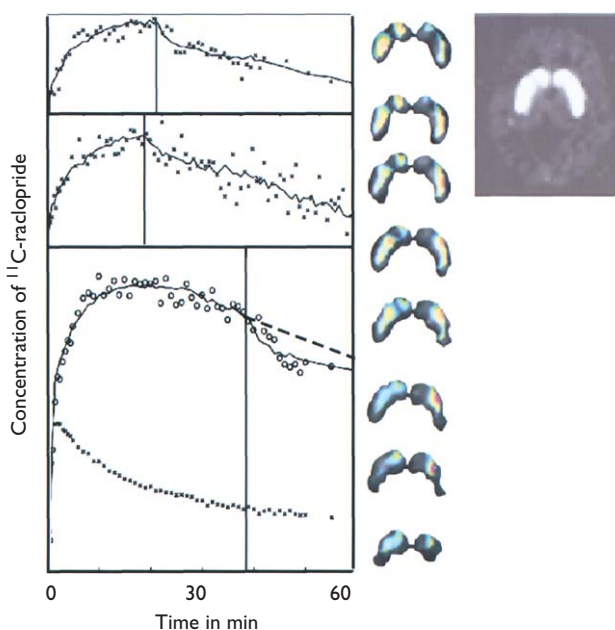
In this model, positive values of  $\gamma$  represent task-related ligand displacement and negative values represent the effect of increase in the rCBF [6]. Hypothesis testing was effected within the framework of the general linear model. The search region was restricted to the striata where the density of  $D_2$  receptors can be imaged with [ $^{11}$ C]raclopride. The null hypothesis  $\gamma \leq 0$  was rejected when  $t > 2.4$  ( $df > 60$ ,  $p < 0.02$ ). To further evaluate the results, we plotted the measured PET concentration history and model fit to data in selected voxels for which the null hypothesis was rejected. Following the fitting process, the displacement rate was examined in each voxel and those with significantly increased dopamine release rate were color coded to form maps of task-related neurotransmission (Fig. 1).

## RESULTS AND DISCUSSION

Mean reaction time during the finger opposition task was  $410 \pm 112$  ms. Immediately after initiation of the task, significant increase in the rate of displacement of [ $^{11}\text{C}$ ]raclopride from the striatal dopamine receptor sites was observed in the caudate and in the mid and posterior putamen bilaterally (Fig. 1). Significantly, dopamine release was detected in the same area of the striatum in all subjects individually. We used different time lags between ligand administration and task initiation in different subjects to ensure that the effect is due to task performance. The ligand displacement was observed within 1 min of task initiation in all subjects. The dissociation rate returned to the baseline in about 10 min. The kinetic model fit the data best when the displacement effect was described as a decreasing exponential with a  $\sim 3$  min half-time. To our knowledge, this is the first study that characterizes the temporal attributes of a neurotransmitter released during a behavioral task. Independent of kinetic modeling, the graph of PET data in Fig. 1 demonstrates more rapid clearance of ligand immediately following task initiation. When data were analyzed with least-squares fitting, we determined that the clearance half-time for the task was on the order of 3 min and  $\tau$  was set to  $0.22 \text{ min}^{-1}$ . In the multi-activation task in which subjects performed two blocks of motor task with different finger mappings, clear evidence of ligand displacement could only be demonstrated in the first block. Observations from previous human [13] and animal studies have also found greater striatal activation and neuronal firing during initial task performances [18].

Since the displacement of [ $^{11}\text{C}$ ]raclopride has been shown to be linearly related to the amount of endogenous dopamine released [19], the results provide evidence of striatal dopamine release during performance of an unrewarded motor task. The finding is in agreement with the observations of the neuroimaging studies that have reported increased striatal activations in similar tasks [4,13]. These experiments have reported increased activation in the putamen, particularly in its mid and posterior parts, where we obtained evidence of dopamine release. It therefore appears that the activities reported in the neuroimaging experiments pertain to those associated with the release of dopamine. These findings are supported by the observations of impaired performances in nonhuman primates following lesions of the putamen [20]. Thus, the evidence from all three methods, neuroimaging, lesion, and the PET, converge to suggest that dopaminergic neurons of the putamen are involved in the processing of unrewarded motor tasks.

In the present experiment, in addition to the putamen, increased [ $^{11}\text{C}$ ]raclopride displacement was observed in the caudate. Activation in the caudate has been consistently reported by the neuroimaging studies when the task requires learning of motor sequences [21]. It has therefore been suggested that the caudate is associated with motor learning [1,5]. A number of experiments, however, have reported activation in this area (along with the putamen) in tasks that involve performance of learned motor sequences that do not involve learning of a new motor sequence, for example, the finger opposition task [4,13]. Since it has been shown that the retrieval of a learned item involves concurrent encoding (learning) processes [22], it is unclear



**Fig. 1.** Column I shows the PET concentration histories and least-squares fits (solid lines) for [ $^{11}\text{C}$ ]raclopride in the left putamen of three different subjects who performed a single unrewarded motor task. For comparison, the lowest curve shows the PET concentration history in a region devoid of specific binding (cerebellum). In the lowest panel on the right, the dashed line indicates the model prediction (see text for equation) assuming no task-induced dopamine release. The vertical lines indicate times of the task initiation. The middle column shows the fusion of raclopride binding potential and a  $t$ -map showing areas of significant change ( $t > 3.0$ ) in the rate of ligand displacement as horizontal sections of the striatum from the dorsal to ventral aspect in 2.4 mm steps (left striatum on the right). For comparison, the inset on the right shows a single horizontal section (including caudate and putamen) of raclopride binding potential. Most significant differences are coded red and the concentration of [ $^{11}\text{C}$ ]raclopride is expressed as  $\text{Bq}/\text{cm}^3$ .

whether the caudate activation observed in the present experiment and in the neuroimaging studies is elicited by the processes associated with concurrent learning of the finger mapping, or by those associated with the planning and execution of motor movements. The caudate activation could also be due to the fact that the task used in the present experiment involved a stimulus-driven response selection process. Neuroimaging studies suggest that this process involves the anterior cingulate, which has strong connectivity with the medial (and ventral) caudate nucleus in the monkeys [23].

Another interesting finding of the present study is the observation of ligand displacement bilaterally, even though the task was performed unilaterally. Neuroimaging studies have reported both, unilateral [13], or bilateral [4], activations of striatum during unilateral task performances. Neuroanatomical and electrophysiological evidence, however, suggests that the striatum receives strong bilateral projections from the supplementary motor area, which is believed to be associated with the volitional aspect of motor planning and movement [24]. Since the dorsal striatum receives most of its motor signals from this area [25], unilateral activation of the supplementary motor area is expected to activate striatum bilaterally [4].

As discussed previously, because of its strong association with rewarding stimuli (for recent review see [9]), many investigators have suggested that the striatal dopamine system is involved only with the motor tasks that are associated with a reward, and not with the unrewarded motor tasks [9,12], even though neuroimaging experiments have consistently shown increased activation in unrewarded motor tasks. The results of the present experiment do not support this view and indicate that the increased striatal activation observed in neuroimaging studied during unrewarded motor tasks [4,13] represents activity of dopaminergic neurons.

The striatal sites where we observed dopamine release are, however, distinct from those that have been implicated in the rewarding motor tasks. The activated sites in the present experiment are located dorsal to the areas that are implicated in the reward-related movements [9–11]. It appears that the striatal dopaminergic neurons have functional specificity for rewarded and unrewarded motor tasks. Neurons located in the dorsal aspect of the neostriatum support unrewarded movements while those located more ventrally are involved in the rewarded movements. This hypothesis is consistent with the functional neuroanatomy of the striatum. Since the cortico-basal ganglia loops originating from the motor areas terminate in the putamen, and those arising from the association cortex and limbic system are connected with the structures located ventrally, i.e. the head of the caudate and the ventral striatum [25], the putamen is more appropriately placed to carry out nonrewarding motor tasks that have little or no cognitive and hedonic component. On the contrary, the reward-based tasks that involve relatively greater cognitive and hedonic processing could be better processed at the structures that are connected with the association cortex and the limbic system.

Detection of the release of dopamine in the same striatal areas where increased activity is reported in similar neuroimaging experiments [4,13] suggests that the PET method used in this experiment is sensitive enough not only to detect dopamine release, but also to localize the areas of activity. As discussed above, the method is also sufficiently sensitive to characterize the temporal attributes of dopamine release. The present study therefore demonstrates, for the first time, that the striatal dopamine system is associated with the processing of unrewarded motor tasks in human volunteers.

## CONCLUSIONS

The results demonstrate that the striatal dopamine is released during performance of an unrewarded motor task. This finding is consistent with the observation of the neuroimaging studies that have reported increased activation of the basal ganglia in this task. The results also demonstrate that the PET technique used in this experiment can be used to extend the findings of the conventional neuroimaging studies that do not provide information about signal transduction.

## REFERENCES

1. Brooks DJ. *J Neural Transm* **108**, 1283–1298 (2001).
2. Jahanshahi M, Jenkins IH, Brown RG *et al.* *Brain* **118**, 913–933 (1995).
3. Playford ED, Jenkins IH, Passingham RE *et al.* *Ann Neurol* **32**, 151–161 (1992).
4. Scholz VH, Flaherty AW, Kraft E *et al.* *Brain Res* **879**, 204–215 (2000).
5. Jueptner M, Frith CD, Brooks DJ *et al.* *J Neurophysiol* **77**, 1325–1337 (1997).
6. Samuel M, Ceballos-Baumann AO, Boecker H and Brooks DJ. *Neuroreport* **12**, 821–828 (2001).
7. Perry EK and Perry RH. *Brain Cogn* **28**, 240–258 (1995).
8. Lange KW, Wells FR, Jenner P and Marsden CD. *J Neurochem* **60**, 197–203 (1993).
9. Schultz W. *Neuron* **36**, 241–263 (2002).
10. Pappata S, Dehaene S, Poline JB *et al.* *NeuroImage* **16**, 1015–1027 (2002).
11. Koeppe MJ, Gunn RN, Lawrence AD *et al.* *Nature* **393**, 266–268 (1998).
12. Lawrence AD and Brooks DJ. *Neurology* **52**, A307 (1999).
13. Boecker H, Ceballos-Baumann A, Bartenstein P *et al.* *NeuroImage* **17**, 999 (2002).
14. Ouchi Y, Yoshikawa E, Futatsubashi M *et al.* *J Cerebr Blood Flow Metab* **22**, 746–752 (2002).
15. Morris ED, Fisher RE, Alpert NM *et al.* *Hum Brain Mapp* **3**, 35–55 (1995).
16. Fisher RE, Morris ED, Alpert NM and Fischman AJ. *Hum Brain Mapp* **3**, 24–34 (1995).
17. Alpert NM, Badgaiyan RD and Fischman AJ. *Neuroimage* **19**, 1049–1060.
18. Graybiel AM, Aosaki T, Flaherty AW and Kimura M. *Science* **265**, 1826–1831 (1994).
19. Breier A, Su TP, Saunders R *et al.* *Proc Natl Acad Sci USA* **94**, 2569–2574 (1997).
20. Miyachi S, Hikosaka O, Miyashita K *et al.* *Exp Brain Res* **115**, 1–5 (1997).
21. Menon V, Anagnoson RT, Glover GH and Pfefferbaum A. *Am J Psychiatry* **158**, 646–649 (2001).
22. Buckner RL, Wheeler ME and Sheridan MA. *J Cogn Neurosci* **13**, 406–415 (2001).
23. Eblen F and Graybiel AM. *J Neurosci* **15**, 5999–6013 (1995).
24. Middleton FA and Strick PL. *Brain Cogn* **42**, 183–200 (2000).
25. Alexander GE and Crutcher MD. *Trends Neurosci* **13**, 266–271 (1990).

Acknowledgement: R.D.B. acknowledges the support of the NIH grant T32CA09362, and Dupont-Warren Foundation.