

Explicit motor memory activates the striatal dopamine system

Rajendra D. Badgaiyan^{a,b}, Alan J. Fischman^{a,b} and Nathaniel M. Alpert^a

^aDivision of Nuclear Medicine, Massachusetts General Hospital and Harvard Medical School and ^bShriners Hospital for Children, Boston, Massachusetts, USA

Correspondence to Dr Rajendra D. Badgaiyan, Division of Nuclear Medicine (White 427), Massachusetts General Hospital, 55 Fruit Street, Boston, MA 02114, USA

Tel: +1 617 724 1793; +1 617 623 1140; fax: +1 617 726 6165; +1 617 623 1140; e-mail: rajendra@wjh.harvard.edu

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We studied the pattern of striatal dopamine release during performance of an explicit motor memory task in healthy volunteers. The release was estimated by dynamically measuring concentration of a dopamine ligand using a positron emission tomography camera. An increased release of endogenous dopamine in the dorsomedial aspect of posterior putamen and in the anterior part of the caudate bilaterally was observed, during task performance.

As we have earlier observed dopamine release in all of these areas, except the right putamen, in an implicit motor memory task, it seems that the striatal dopaminergic network for implicit and explicit motor memories are essentially similar. *NeuroReport* 19:409–412 © 2008 Wolters Kluwer Health | Lippincott Williams & Wilkins.

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Introduction

Two forms of motor memory, implicit (nonconscious) and explicit (conscious), are distinct in several cognitive parameters [1]. It is, however, not clear whether these memories are processed by a single neural network (e.g. [2]), or by distinct separable networks (e.g. [3]). On the basis of the observation of nonoverlapping regions of activation, a number of neuroimaging studies have concluded that implicit and explicit motor memories are processed by two distinct networks [4,5]. It has, however, been argued that activation in distinct brain regions could be due to differences in training regimen or task difficulty [6], because largely overlapping areas of activation in the caudate, prefrontal and medial temporal areas are observed in both implicit and explicit conditions when the methodological biases are reduced [7,8]. Even though the precise role of these structures is unclear, the medial prefrontal cortex is generally associated with the explicit, and the striatum with implicit motor memory. This association, however, gets complicated because activation in both of these regions is reported in both the implicit and explicit conditions [7,8].

On the basis of these findings, investigators who favor multiplicity of network have suggested (e.g. [9]) that the striatum and the medial prefrontal cortex interact in such a way that the cortex exerts control on activity of the striatum during explicit retrieval, whereas the activity of these regions is uncoupled when learning is essentially implicit. Those who favor unitary network (e.g. [6]) suggest that modulation of the medial prefrontal cortex on striatal activity in the explicit condition is not unidirectional and

an interactive functional circuit between these structures is selectively engaged in the explicit condition.

The present experiment was designed to acquire additional data needed to understand the brain network that controls implicit and explicit motor memories. We have recently demonstrated that dopamine is released in the caudate and left putamen during performance of an implicit motor memory task [10]. We used this finding in the present experiment to examine whether dopamine neurotransmission is differentially activated in explicit motor memory. As a change in the experimental paradigm would introduce additional variable, we used the same paradigm that was used in the implicit motor memory experiment [10].

This experiment is important because the role of dopamine in the processing of explicit motor memory is unclear. Studies conducted on patients with dysregulated dopaminergic system have reported contradictory data suggesting either intact [11] or deficient [12] performance.

For detection of task-induced release of striatal dopamine, we used the molecular imaging technique [13] that was used in an earlier implicit motor memory experiment [10]. After volunteers had studied a sequence of movements in a modified serial reaction time (SRT) task, they received intravenous injection of a dopamine receptor ligand ¹¹C-raclopride. Immediately after the injection, an explicit motor memory task was initiated and the ligand concentration was measured dynamically using a positron emission tomography (PET) camera. As the ligand is competitively displaced from receptor sites by endogenously released dopamine, a reduction in its concentration indicated task-induced release of dopamine [13,14].

Methods

The experiment was conducted on six young, healthy, right-handed volunteers (mean age 21.8 ± 2.7 years; three men and three women) who had no history of a psychiatric or neurological disorder. The modified SRT task included three conditions: study, control and test. In the study condition, volunteers were shown four boxes (2.5×2.5 cm) on a computer monitor. An asterisk appeared sequentially in one of these boxes every 1250 ms for 250 ms. Volunteers were asked to press a key that corresponded to the location of the marked box and to remember the sequence of motor movements. The sequence (2-3-1-4-3-2-4-1-3-4-2-1) had 12 elements in which each position had the same frequency and there were no direct repetitions, runs or trills of more than three positions in a row [10]. After 60 repetitions, volunteers recalled the sequence using the procedure used in the test condition (described below). After the study, volunteers were positioned before the camera and the ligand ^{11}C -raclopride was administered. The control condition was started immediately after the injection. In this condition, stimuli appeared in one of the four boxes randomly, and the task was to indicate location of the marked box as quickly as possible, using a keyboard. After 25 min, the control condition was terminated and the test condition began. In this condition, stimuli were presented in the sequence that was learned in the study. Each stimulus was presented for 250 ms after a delay of 1000 ms. During the delay, volunteers predicted location of the next stimulus and pressed a corresponding key before the stimulus appeared. The stimulus presentation time and frequency were same in the control and test conditions. Accuracy and reaction time were recorded in each trial.

Procedures for acquisition and analysis of PET data were similar to those used in the study on implicit motor memory [10]. After volunteers were positioned before the camera (ECAT EXACT HR+, Siemens), a single intravenous bolus of 10–15 mCi of the ligand ^{11}C -raclopride was administered intravenously over a period of 60 s. The data were acquired in 30 s epochs during the first 5 min and in 60 s epochs thereafter. The PET images were reconstructed using a standard three-dimensional filtered back projection algorithm with corrections for photon attenuation, random coincidences and scatter and dead time. To minimize motion artifact, images were registered to a common orientation and using a transformation matrix all frames were aligned to a reference frame. Thereafter, a voxelwise analysis was carried out using a kinetic model that is designed to detect transient changes in ligand displacement [13]. The results were then averaged across volunteers by summing the data of each volunteer and elastically registering them to a standard template (using SPM99). A voxelwise t -map was then computed to localize voxels where the rate of ligand displacement increased significantly ($t > 3.0$) after task initiation (test condition). Finally, time–activity curves were obtained from these voxels and from the cerebellum, which was used as a reference region because of paucity of dopamine receptors in this region.

Results

The response accuracy was greater ($P < 0.001$; t -test) in the control condition (mean: $98.30 \pm 0.85\%$) as compared with the test (mean: $93.83 \pm 1.77\%$), but there was no significant

difference in the reaction time recorded in the test (mean: 415 ± 104 ms) and control (mean: 469 ± 119 ms) conditions.

We observed a significant increase ($t > 3.0$) in the rate of ligand displacement in the test condition. As endogenously released dopamine competitively displaces the ligand from receptor sites [13], the observation indicated that dopamine was released during task performance. A voxelwise t -map constructed after averaging the data across volunteers (Fig. 1) revealed significant displacement in the dorsomedial aspect of posterior two-third of putamen bilaterally (peak t =right 3.80; left 3.38), and in the anterior part of the body of caudate (peak t =right 3.48; left 3.52). To ensure that the increased rate was due to receptor–ligand interaction and not because of globally increased clearance of

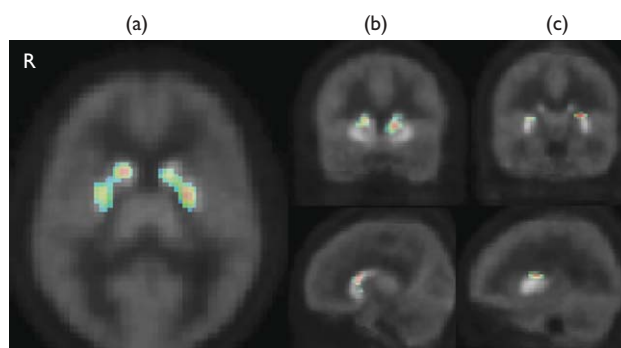


Fig. 1 Dopamine was released in the anterior part of the body of caudate (a and b) and in the dorsomedial putamen (a and c) during performance of an explicit motor memory task. The t -maps show the striatal areas where a significant change ($t > 3.0$) in the rate of ligand displacement was observed during task performance.

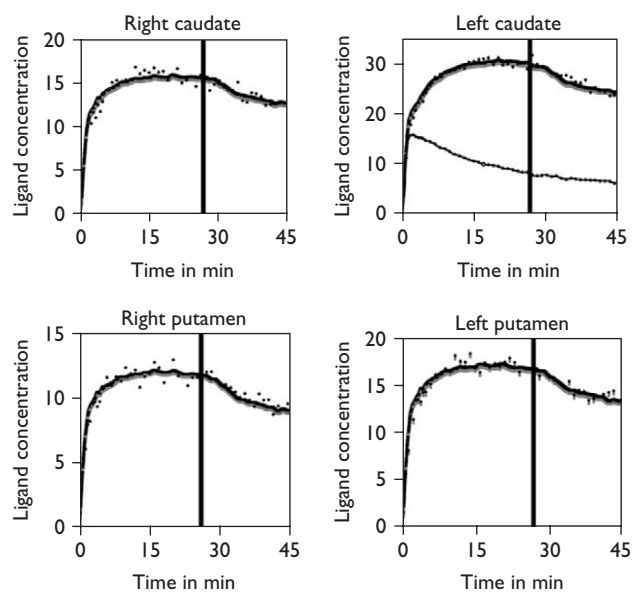


Fig. 2 The time–activity curves show the concentration histories (circles) and least square fits (solid lines) for the ligand (^{11}C -raclopride) in the anterior part of the body of caudate and dorsomedial aspect of posterior putamen. The rate of ligand displacement increased significantly after task initiation (vertical lines). The positron emission tomography concentration history of the reference region (cerebellum) is shown in the upper right panel (lower curve). The rate of ligand displacement did not change significantly in this region.

nonspecifically bound ligand, we measured the ligand concentration in the reference region (cerebellum). No significant change in the rate of ligand clearance in this region at any time during the experiment was observed (Fig. 2). This measurement indicated that the changes observed in the striatal areas were due to dopamine-induced displacement.

Discussion

Dopamine release in all three striatal areas where the neurotransmitter was released during processing of implicit motor memory in an earlier study [10] is a significant finding of this experiment. It suggests that implicit and explicit motor memories are processed by the same striatal dopaminergic network. The additional activation in the right dorsomedial putamen, observed in the explicit but not in the implicit condition, indicates that an additional processing step is needed in the explicit condition.

The finding that implicit and explicit motor memories share a common dopaminergic network is in agreement with the studies that have indicated virtual inseparability of the networks [6]. Some of these studies have used laboratory procedures that allow separation of implicit and explicit components in a memory task. A commonly used objective measure uses the process dissociation procedure. In this procedure, after volunteers have completed a memory task (e.g., SRT task), they are asked to generate the learned sequence under inclusion and exclusion conditions. In the inclusion condition, the sequence is recalled explicitly but the performance can be affected by implicit knowledge if forgotten elements of the sequence are filled in by guessing. The exclusion condition involves generation of sequences that do not contain fragments of the learned sequence. Inclusion of the learned sequence in this condition indicates implicit learning. Initial studies that used this procedure in the SRT task [15] indicated that there is minimal explicit memory contamination if stimuli are presented immediately after the response. If the response to stimulus interval is set at 250ms, however, there is a significant explicit memory contamination. As subsequent studies have not been able to replicate these findings, separability of the two forms of memory remains unsettled [16].

In addition to the nonreplicability, results of these experiments are complicated by conceptual issues concerning expression of explicit and implicit knowledge, particularly if the knowledge is weak and falls in the category of fringe consciousness or 'feeling of knowing'. As these conditions have both explicit and implicit components, it is unclear whether the responses based on the feeling of knowing in inclusion and exclusion conditions are driven by implicit or explicit memory (for a discussion, see Ref. [17]). Thus, on the basis of these data, it is difficult to draw a conclusion concerning separability of the brain mechanisms that process implicit and explicit motor memories. Neuroimaging studies have also failed to arrive at a conclusion. These studies have reported contradictory findings, suggesting either nonoverlapping [4,5] or overlapping [7] regions of activation in the implicit and explicit conditions. Our observation of overlapping areas (bilateral caudate and left putamen) of striatal dopaminergic activity is consistent with the findings of experiments [6,7,16,17] that suggest unitary network. As the data of this study, however, pertains

only to the striatum, no conclusion concerning separability of the cortical network can be drawn.

In addition to the overlapping areas, we observed an additional activation in the right dorsomedial putamen in the explicit condition. As this activation was not observed in the implicit task [10], it seems that an additional processing step is required in the explicit condition. It is consistent with the finding of a recent functional MRI experiment, which reported additional processing involving the frontostriatal network in the explicit condition [6]. The present results indicate that the additional processing is mediated by the dopaminergic system. In this context, the observation that the explicit component of an implicit motor memory task is enhanced when volunteers are rewarded for correct scores is important [18]. As the striatal dopaminergic system is activated in reward processing [19], enhancement of explicit memory during reward processing could be associated with the activated dopaminergic system.

The results indicate that activation of the left putamen (along with bilateral caudate) is adequate if a task involves only implicit motor memory, but if it requires elicitation of explicit memory, the right putamen is also activated. Further, because striatal areas that process implicit memory were activated during explicit retrieval, it is possible that activation of implicit memory is inherent in explicit memory tasks. We have previously arrived at a similar conclusion in a cued-recall task [20].

A comparison of the data of the present experiment with those acquired in previous molecular imaging studies provides an insight on dopaminergic processing of motor cognition. We have earlier reported that dopamine is released in the left dorsomedial putamen and the right caudate during processing of a motor planning task [14]. Significantly, dopamine release in these areas was observed in both implicit [10] and explicit motor memory (present study) tasks. As all three tasks involve planning of motor movements, it seems that dopaminergic activities in the left putamen and right caudate are associated with motor planning [10,14]. Furthermore, because implicit motor memory activated an additional area in the body of the left caudate [10], we suggested that this activation is associated with detection of a change in sensory environment (change from random to sequential presentation of stimuli), and with formulation of new rules based on the changed environment (context). As present experiment also involves both processing, observation of the left caudate activity is consistent with our earlier findings and conclusions concerning role of the left caudate [10].

Bilateral activation of the dorsomedial putamen in this experiment and unilateral activation in the implicit memory task provides further insight. The dorsomedial putamen and the anterior part of the body of caudate, which are activated in both implicit and explicit tasks, receive inputs from the ventrolateral prefrontal cortex (VLPFC), supplementary motor area (SMA) and the premotor area (PMA) [21]. Interestingly, all of these areas are associated with learning. Thus, the VLPFC plays a major role in selection of the most appropriate act among alternative competing motor acts on the basis of conditional operations [22]. Involvement of the SMA is indicated by a positive correlation between its volume and performance in SRT tasks [23]. Furthermore, there are reports suggesting that there is a significant correlation between the degree of learning and learning-related changes in firing patterns of

the SMA and PMA [24]. In addition, the observation of a positive correlation between learning-related activation of the PMA and VLPFC, and occupancy of striatal dopamine transporter, indicates that the mnemonic functions of these structures are dopamine dependent [25]. It seems that the output from these cortical areas is enhanced in explicit memory. As a result of this enhancement, in the present experiment there was bilateral activation of the dorsomedial putamen (as opposed to unilateral activation in the implicit condition), which receives learning-related signals from the PMA and VLPFC [21].

Conclusion

The results suggest that the striatal dopaminergic network activated during processing of explicit and implicit motor memories are essentially the same. The explicit memory, however, requires an additional processing step and enhanced activation of the network. We have discussed earlier [10] that dopaminergic modulation of motor memory involves two mechanisms. The first mechanism is mediated by the left caudate and is responsible for detection of a change in the context, and the second mechanism involves the putamen and right caudate. This mechanism facilitates response execution by modifying the network that controls motor planning.

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