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Differential activation of dorsal basal ganglia during externally and self paced sequences of arm movements

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THE basal ganglia are thought to be critically involved in motor control. However, the relative contributions of the various sub-components are not known. Although, in principle, functional magnetic resonance imaging (fMRI) provides adequate resolution to image the basal ganglia at the spatial scale of the individual nuclei, activating these nuclei with fMRI has proven to be difficult. Here we report two tasks, involving externally and self paced sequences of arm movements, which resulted in significant activation of contralateral posterior (postcommissural) putamen and globus pallidus. This activation did not significantly differ between the tasks. In contrast, significant activation of the contralateral and ipsilateral anterior caudate and anterior putamen was observed only during externally paced arm movements. These results suggest a dissociation in the roles of the anterior and posterior dorsal basal ganglia: the anterior caudate and putamen may be involved in sensory to motor mapping and the posterior putamen and globus pallidus may be involved in the motor response itself. The findings support the hypothesis that the basal ganglia may be involved in gating sensory influences onto motor areas .*NeuroRepor t* 9: 1567–1573 © 1998 Rapid Science Ltd.

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Introduction

The dorsal striatum and globus pallidus are thought to play an important role in movement initiation, control and sequencing.[1] Thus, for example, patients with Parkinson's disease, which is characterized by depletion of striatal dopamine, have difficulty with self-initiated or volitional movements.[2] A potentially powerful approach to investigating the motor function of the dorsal basal ganglia has been to examine differences between self and externally paced movements. Romo *et al*[3] examined the anterior striatum in monkeys performing self-initiated and stimulus-triggered arm reaching movements and found a segregated population of neurons engaged in internally generated movements. More importantly, they also report that more neurons were active during externally triggered movements. On a larger spatial scale, several positron emission tomography (PET) studies have examined lentiform nucleus (putamen and globus pallidus) activation during motor tasks that involved self-initiated or self-paced and externally triggered movements in neurologically normal subjects. These studies found differences in activation in the dorsolateral prefrontal cortex and the supplementary motor area but not in the lentiform nucleus.[4–6] Thus, for example, Deiber *et al*[6] found no differences in left lentiform nucleus activation when directions of joy stick movements were cued by the pitch of tones, freely selected or always in a forward direction. Reviewing these and a number of other studies has led Brooks[7] to comment that the role played by the basal ganglia in controlling motor function remains enigmatic.

One reason for this negative finding might be that PET studies do not have the effective spatial resolution to distinguish between sub-regions of the basal ganglia nuclei. Functional magnetic resonance imaging (fMRI) provides greater spatial resolution that PET and, in principle, could provide the spatial resolution to differentiate between sub-components of the basal ganglia. However, attempts to activate the putamen and globus pallidus in our and other laboratories with complex finger movements have not been successful. One fMRI study reported activation while subjects performed pronation and supination hand movements.[8] However, this task is not particularly amenable to manipulations in the cognitive, perceptual or motor dimensions.

The aim of this report is twofold. First, and most importantly, to demonstrate fMRI activation of the dorsal basal ganglia during two sequencing tasks, one

involving externally paced arm movements and the other involving self paced arm movements. We hypothesized that the higher motor load involved in making arm (as opposed to finger) movements would result in detectable activation of a region of interest (RoI) that included the dorsal striatum and globus pallidus. Second, to describe the differential activation of sub-regions of the RoI during these tasks and discuss its implications for dorsal basal ganglia function. Both multisubject and single subject data were analyzed.

Materials and Methods

Subjects: Twenty-two healthy right-handed subjects (aged 20–35 years) participated in the study after giving written informed consent. Eleven subjects (six men and five women) performed the externally paced arm movement task while 11 other subjects (seven men and four women) performed the self-paced are movement task. The two groups did not differ significantly in gender ($p > 0.5$; Fisher's exact test).

Experimental design: The tasks consisted of 12 alternating 40 s epochs of rest and arm movements. Subjects rested the closed fist of their right hand on the base of a palm-shaped keypad. Movement consisted of touching, with thumb and forefinger pinched together, the tip of one of four 'fingers' 15 cm away from the base. Subjects were explicitly instructed to avoid finger movement. Subjects practised the task briefly for 2 min and 40 s (four epochs) 30 min before the scan and were monitored visually during the scan to verify consistent task performance.

In the externally paced arm movement task, numbers between 1 and 4 were presented with an ISI of 2 s. Subjects in this group made arm movement to corresponding locations on the keypad after each number. In the self-paced arm movements task group, subjects first mentally generated three numbers between 1 and 4 and then made arm movements to corresponding locations on the keypad, returning to base after each number and repeating this with a new sequence until 40 s elapsed and they were verbally instructed to 'STOP'. After a 40 s rest period they were told to 'BEGIN'. Pilot data had indicated that generating three numbers at a time roughly balanced the number of movements between the two tasks.

The task was programmed using Psyscope[9] on a Macintosh (Sunnyvale, CA) notebook computer. Initiation of scan and task was synchronized using a TTL pulse delivered to the scanner timing microprocessor board from a CMU Button Box microprocessor (http://poppy.psy.cmu.edu/psyscope) connected to the Macintosh. Audio signals were amplified using a home audio receiver, transmitted to a piezo-electric speaker placed near the head of the scanner and then piped binaurally to the subjects.

Acquisition: Images were acquired on a conventional 1.5T GE (Milwaukee, WI) scanner using a quadrature whole head coil. Subjects lay with their head restrained using a bitebar.[10] Twelve axial slices (6 mm thick, 0 mm skip), extending roughly from –10 to 62 mm relative to the anterior commissure, were imaged with a temporal resolution of 4 s at 120 time points using a T2* weighted gradient echo spiral pulse sequence (TR = 1000 ms, TE = 40 ms, flip angle = 40°, 4 interleaves).[11] Field of view was 310 mm and the effective inplane spatial resolution was 4.35 mm. Images were reconstructed, by inverse Fourier transform, for each of the 120 time points into 256 × 256 × 12 image matrices (resolution: 1.21 × 1.21 × 6 mm). Images corresponding to the first two time points were discarded from further analysis to eliminate non-equilibrium effects.

High resolution whole brain images were also acquired to localize activation foci, using a T1-weighted spoiled grass gradient recalled (SPGR) 3D MRI sequence: (TR = 24 ms; TE = 4 ms; flip angle = 40°; 24 cm field of view; 124 slices in sagittal plane; 256 × 192 matrix; acquired resolution = 1.5 × 0.9 × 1.2 mm) reconstructed as a 124 × 256 matrix (resolution: 1.5 × 0.9 × 0.9 mm).

Preprocessing: fMRI data were pre–processed using SPM96 (http://www.fil.ion.bpmf.ac.uk/spm). Images were corrected for movement using least square minimization without higher-order corrections for spin history. Images were normalized to stereotoxic Talairach coordinates and resampled every 2 mm using sinc interpolation.

Region of interest: The region of interest (RoI) consisted of the dorsal striatum and globus pallidus in both hemispheres. In addition to all of the putamen, the dorsal striatum also included the portion of the caudate anterior to the anterior commissure, i.e. in the caudate head. Since each subject's brain was normalized to Talairach space, voxels in the RoI were defined on a Talairach template image. The number of voxels in the RoI in Talairach space was 3008.

Statistical analysis: Individual voxels activated by the tasks was identified using regression analysis as implemented in SPM96.[12–14] A reference waveform consisting of +1 for motor task images and –1 for rest images was used to predict the main effect of

task. To take into account delay and dispersion in the haemodynamic response, the waveforms were convolved with a 6 s delay Poisson function.

Both single subject and multisubject (group) activations were computed. For groups averages the reference waveform was replicated for each subject in a blocked design matrix. The confounding effects of fluctuations in global mean were removed using an ANCOVA model. Low frequency noise was removed with a high pass filter (0.5 cycles/min) applied to the fMRI time series at each voxel. A temporal smoothing function (Gaussian kernel corresponding to dispersion of 8 s) was applied to the fMRI time series to enhance the signal to noise ratio. Voxel-wise t-statistics were computed using multivariate linear regression. The degrees of freedom were adjusted to take into account auto-correlations in the time series and the t-statistics were normalized to Z scores.

To determine individual voxels in the RoI that were significantly active, a Bonferroni correction was applied ($p < 0.05/N$ where $N = 3008$ is the total number of voxels in the RoI). Thus, only voxels with $Z > 4.15$ ($p < 1.66 \times 10^{-5}$) were considered significant.

In order to statistically compare activation within group and between groups we defined the following sub-regions within the RoI based on group activation clusters (see below): anterior caudate, anterior putamen, and posterior putamen plus globus pallidus (putamen + GP). Voxels were considered anterior or posterior with respect the anterior commissure. To investigate within group differences in laterality, the number of Bonferroni-corrected voxels activated in the left and right hemispheres in each of the sub-regions in individual subjects was compared using a paired *t*-test. To investigate inter-group (task) differences, the number of Bonferroni-corrected voxels activated in individual subjects in sub-regions of the RoI was compared using an unpaired *t*-test.

Results

Externally paced movements: Multisubject ($n = 11$) analysis revealed significant clusters of activation in the left and right anterior caudate, the left and right anterior putamen and left posterior putamen + GP (Table 1, top; Fig. 1, left). Figure 2 (top) shows sagittal and coronal views of activation superimposed on high-resolution MRI at the focus of maximal activation in the posterior putamen + GP. This is further elaborated in Fig. 3 where axial views across 15 2 mm planes parallel to the AC-PC axis are shown. The posterior activation extends from the putamen ventrally and medially into the external segment of the globus pallidus.

Significant activation of these subregions was also detected in > 50% of the subjects analyzed individually: eight subjects showed activation in the left and four in the right posterior putamen, six subjects showed activation of the left and anterior caudate and six in the right anterior caudate, seven subjects activated the left and seven the right anterior putamen.

Comparing activations across subjects revealed that left and right caudate activations were not significantly different ($p > 0.5$) nor were left and right anterior putamen activations ($p > 0.6$). Left posterior putamen + GP activation was, however, significantly greater than right putamen + GP activation ($p < 0.03$).

Self-paced movements: Data from one of the 11 subjects contained artifacts and was not used in this study. Multisubject ($n = 10$) analysis revealed significant activation of the left posterior putamen + GP but not the anterior putamen or the anterior caudate (Table 1, bottom; Fig. 1, right). Figure 2 (bottom) shows sagittal and coronal views of activation superposed on high-resolution MRI at the focus of maximal activation in the posterior putamen + GP. Figure 4 shows the group average activations superimposed on axial high-resolution MRI across 15 2 mm planes parallel to the AC-PC axis.

Table 1. Anterior caudate, anterior putamen, and posterior putamen + GP activation in the externally (top) and self paced (bottom) sequencing of arm movement groups. The number of voxels that met Bonferroni threshold (Z > 4.15), location of peak activation and maximum Z score in each hemisphere are shown.

	Left			Right		
Basal ganglia sub-region	No. voxels	Z max	Peak location	No. voxels	Z max	Peak location
Externally paced task						
Anterior caudate	143	7.84	–12,18,12	200	7.76	8,14,4
Anterior putamen	76	7.63	–22,18,2	130	7.34	20,14,8
Posterior putamen and globus pallidus	183	7.52	–30,12,10	10	5.73	30,–16,–4
Self paced task						
Anterior caudate	0	–	–	0	–	–
Anterior putamen	0	–	–	3	4.48	22,12,6
Posterior putamen and globus pallidus	104	6.65	–28,–16,0	0	–	–

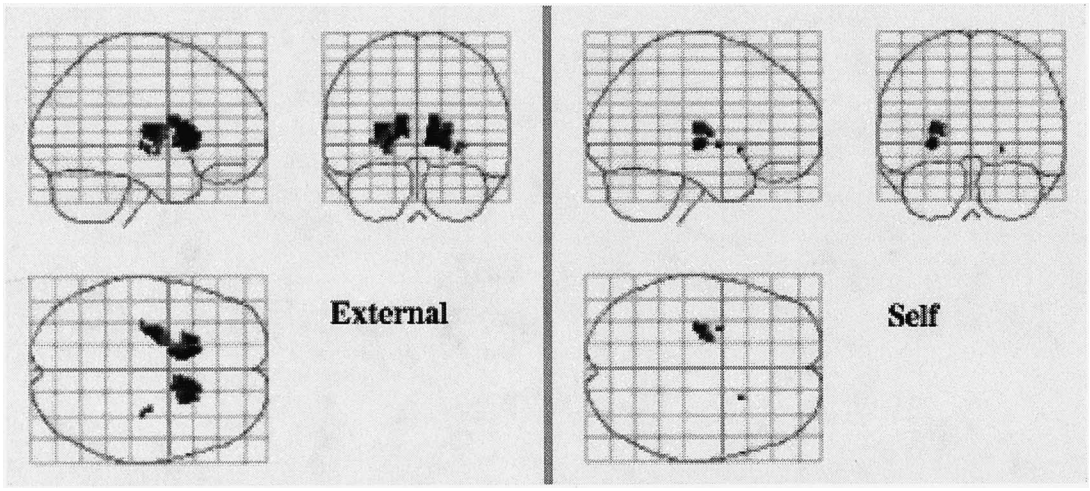

FIG. 1. Maximum intensity projection maps of multisubject activation in externally paced (left) and self-paced (right) arm movement groups show that the anterior caudate and anterior putamen are differentially activated in the externally paced arm movement group. Each voxel shown was significantly activated after Bonferroni correction ($Z > 4.15$; $p < 0.05$).

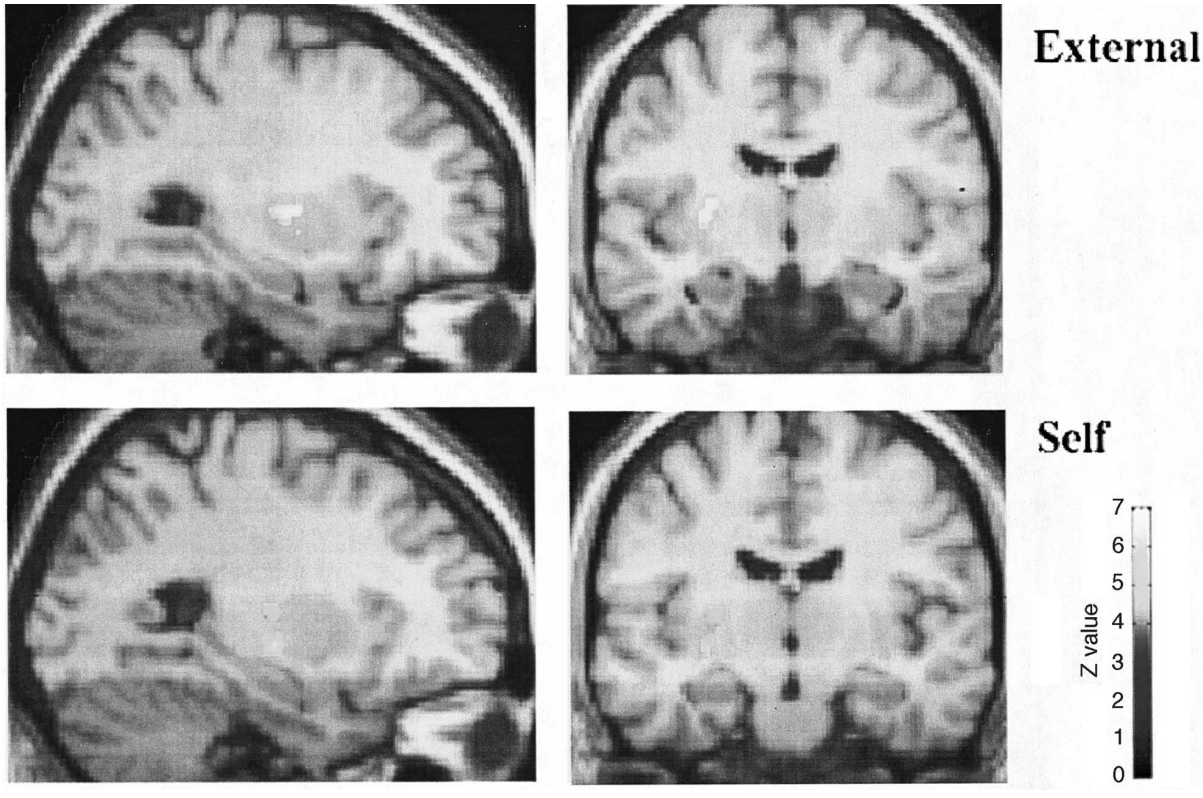

FIG. 2. Sagittal and coronal views of activation superposed on high-resolution MRI in Talairach space. Planes through voxels with maximum activation in the posterior putamen + GP are shown for (top) externally paced arm movements and (bottom) self-paced arm movements. Each voxel shown was significant after Bonferroni correction ($Z > 4.15$; $p < 0.05$).

Significant activation of these sub-regions was also detected in individual subjects. Five subjects showed activation in the left and five in the right posterior putamen + GP, four subjects showed activation of the left and four in the right anterior caudate, five subjects activated the left and three the right anterior putamen.

Comparing activations across subjects revealed that the left and right caudate activations were not significantly different ($p > 0.4$) nor were the left and right anterior putamen activations ($p > 0.2$). The left posterior putamen + GP showed significantly greater activation than the right putamen + GP ($p < 0.05$).

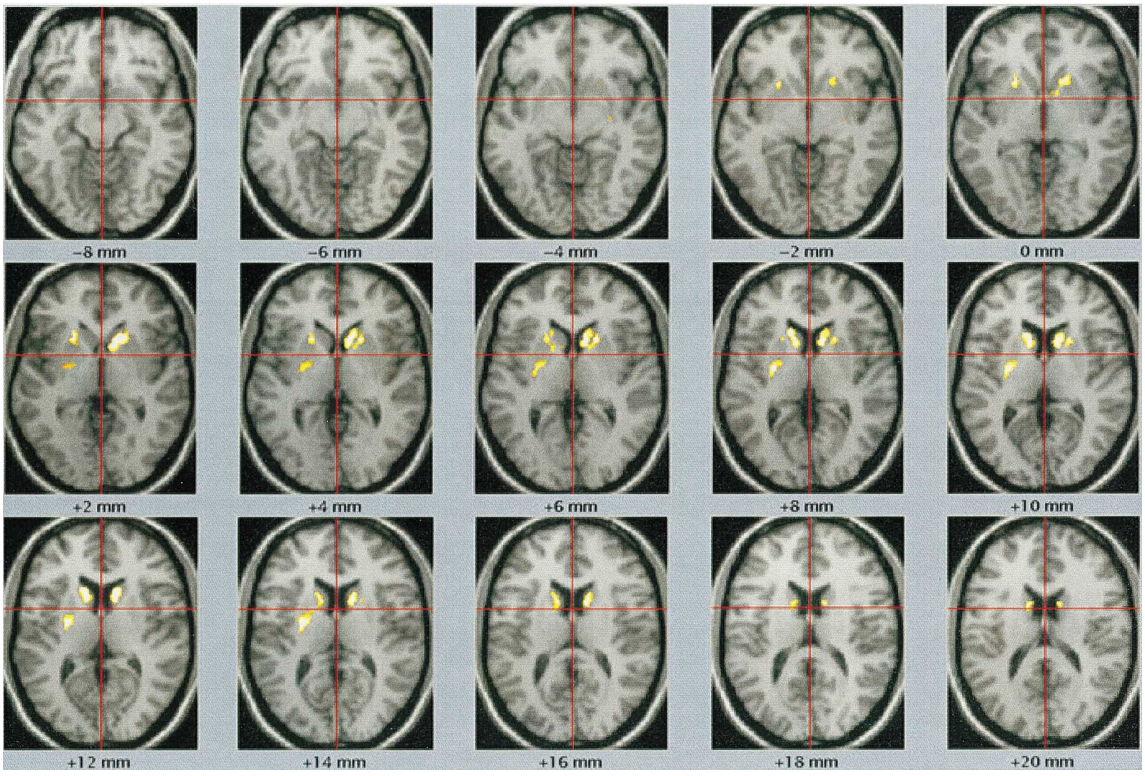

FIG. 3. Activation of anterior caudate, anterior putamen and posterior putamen + GP in the externally paced movement group. Activation maps are shown superimposed on axial high-resolution MRI in Talairach space across 15 planes parallel to the AC-PC axis from –80 to +20 mm. Each voxel shown was significant after Bonferroni correction ($Z > 4.15$; $p < 0.05$). Scale is the same as in Fig. 2.

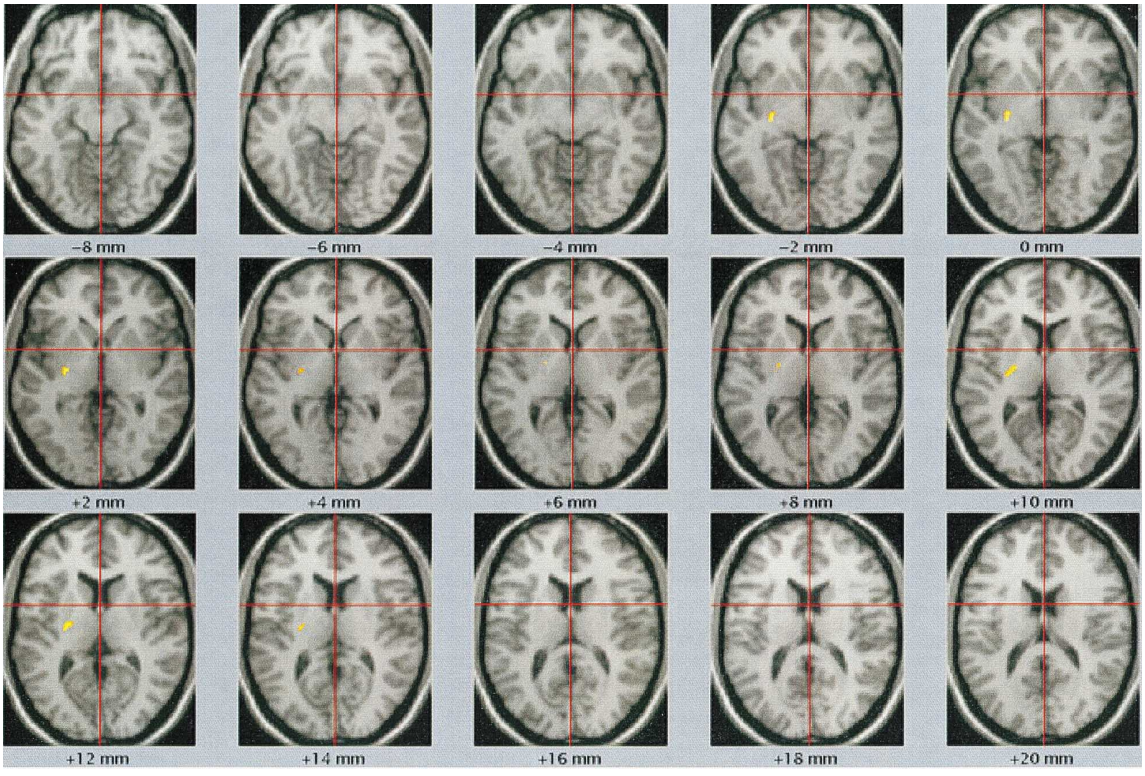

FIG. 4. Activation of posterior putamen + GP in self-paced movement group. Activation maps are shown superimposed an axial high-resolution MRI across 15 planes parallel to the AC-PC axis from –8 to +20 mm. Note that compared to the externally paced arm movement group (Fig. 3), there is hardly any activation of the anterior caudate and anterior putamen. Each voxel shown was significant after Bonferroni correction ($Z > 4.15$; $p < 0.05$). Scale is the same as in Fig. 2.

Comparison of externally and self-paced movements: The unpaired *t*-test was used to compare the number of voxels activated, above the Bonferroni corrected threshold, between the externally and self-paced task groups. Anterior caudate (sum of both hemispheres) activation was significantly greater in the externally than self paced group ($p < 0.04$). Similarly, anterior putamen activation was significantly greater in the externally paced group ($p < 0.02$). Left posterior putamen + GP activation was not significantly different between the groups ($p > 0.2$) nor was the right posterior putamen + GP activation ($p > 0.8$). The sum of left and right posterior putamen+GP activation was also not significantly different between the groups ($p > 0.3$).

In summary, both the anterior caudate and the anterior putamen showed significantly greater activation during externally compared to self-paced movements.

Discussion

Both externally and self-paced arm movements resulted in significant fMRI activation of the dorsal basal ganglia. The activations reported in this study met a conservative Bonferroni correction for the number of voxels in the RoI ($p < 1.66 \times 10^{-5}$). Our analysis approach allowed us to detect not only whether the RoI was activated by the tasks but also to address the question of which specific sub-region or hemisphere within the RoI was significantly activated and the manner in which activations differed between tasks.

Both the externally and self-paced arm movements significantly activated the left posterior (post-commissural) putamen + GP. In the sub-region, the peak activation was located in the left putamen, about 6 mm above the AC-PC axis, and extended ventrally and medially into the external and internal segments of the globus pallidus to 4 mm below the AC-PC axis. In comparison, only a few voxels were activated in the right hemisphere. The left posterior putamen + GP activation is in close proximity to sites lesioned, during pallidotomy, to reduce the motor sequencing deficits of Parkinson's disease.[15] The putamen activation appears to correspond most closely with projections from the arm region of the motor cortex mapped out in primate labelling studies.[16] The two tasks did not differ significantly in their activation of either the left or right posterior putamen + GP.

In contrast, the anterior caudate and anterior putamen were significantly activated in the externally paced group but not in the self-paced group. As the group averages show, few voxels were activated in the self-paced group in the anterior putamen and more strikingly, no voxels were active in the anterior caudate at the Bonferroni adjusted threshold. Left and right hemisphere activations in these regions were not significantly different in either group.

In summary, the two tasks differentially activated the anterior caudate and anterior putamen but not the posterior putamen + GP: i.e. both externally paced and self-paced movements activated the posterior putamen + GP but only the externally paced movements activated the anterior caudate and putamen. A key difference between the two tasks is the requirement to map sensory input to the appropriate motor response present in the externally paced but not the self paced task. These observations suggest an important dissociation in the roles of the anterior and posterior dorsal basal ganglia. The anterior caudate and putamen may play an important role in sensory to motor mapping, whereas the posterior putamen + GP may be related to motor execution itself. This interpretation is supported by the fact that while the anterior activation was bilateral, the posterior activation was larger on the left (contralateral). Lidsky *et al.*[17] have suggested that one of the functions of the basal ganglia is to gate sensory influences onto motor areas. We suggest that the anterior caudate and anterior putamen may play such a role. Electrophysiological studies have shown that striatal neurons are responsive to sensory stimuli.[18] Moreover, recording in cats, Manetto and Lidsky[19] found that neurons in the caudate nucleus were active only during sensory-triggered movements but not movement in general – sensory stimulation was a necessary but not a sufficient condition for caudate unit responding and stimuli caused unit responses only when movements were evoked.

This is also consistent with neuroanatomical evidence indicating that the dorsal striatum is not strictly a motor structure and that it consists of distinct association and sensorimotor territories.[20] The association territory, comprising the part of the putamen anterior to the anterior commissure and large parts of the caudate head, receives projections from various frontal (excluding motor and premotor areas), temporal and parietal lobes.[21] The sensorimotor striatal territory, comprising the dorsolateral sector of the post-commissural portion of the putamen, receives projections from the somatosensory, motor and premotor cortices. Thus, auditory to motor mapping and execution of motor movements might be processed in predominantly segregated regions in the striatum and then reprojected to motor and premotor cortices via the globus pallidus and the ventral-anterior and ventral-lateral thalamic nuclei. Consistent with the present findings, Miyachi *et al.*[22] found that inactivation of the monkey anterior striatum resulted in deficits in learning new stimulus to response mappings

and inactivation of the posterior putamen resulted in deficits in execution of motor responses. We hypothesize that interactions between the anterior and posterior dorsal striatum might play an important role in binding sensory inputs to motor responses.[1]

One of the advantages of fMRI is that individual subjects can be investigated. In single subjects, activation of the left posterior putamen + GP during externally paced arm movements was the most consistent finding with eight of 11 subjects activating this region. In this study, we did not attempt to separate the activations of the posterior putamen from that of the external and internal segments of the globus pallidus. High resolution imaging with 3–5 T MRI scanners should enable further studies of the differential contributions of these structures to motor sequencing and function.

Conclusions

Several previous fMRI studies involving finger movements have failed to report activation of the basal ganglia. Increased motor demands of making arm movements may have resulted in the activation observed in the present study. More broadly, the findings suggest that differential contributions of basal ganglia structures during motor sequencing can be investigated using fMRI. Motor, perceptual and cognitive manipulations of these tasks may help future investigations of the contributions of the basal ganglia nuclei to motor control, learning and cognition.

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