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Striatal dopamine release induced by repetitive transcranial magnetic stimulation of the human motor cortex

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Summary

Brain dopamine is implicated in the regulation of movement, attention, reward and learning. Dysfunction of dopamine plays a role in Parkinson's disease, schizophrenia and drug addiction. It is released in the striatum when dopamine neurons in the midbrain undergo burst firing. Several animal studies have shown that dopamine can also be released under direct control of glutamatergic corticostriatal efferents. However, the existence and physiological significance of this mode of action remain controversial. We have shown previously that repetitive transcranial magnetic stimulation (rTMS) of the human prefrontal cortex led to focal dopamine release in the ipsilateral caudate nucleus, supporting the corticostriatal mode of dopamine release. Using the same experimental approach, we sought to confirm this hypothesis. We used [^{11}C]raclopride and PET to measure changes in extracellular dopamine concentration following rTMS of the motor cortex in six healthy human subjects. rTMS of the left primary motor cortex caused a reduction in [^{11}C]raclopride binding in the left putamen compared with rTMS of the left occipital cortex. There were no changes in binding in the right putamen, caudate nucleus or nucleus accumbens. The area of statistically significant change in binding corresponded closely to the known projection zone of corticostriatal efferents originating in monkey motor cortex. This finding has implications for the functional role of subcortical dopamine.

Keywords: transcranial magnetic stimulation; basal ganglia; motor cortex; raclopride; dopamine

Abbreviations: BP = binding potential; M1 = primary motor cortex; OCC = occipital cortex; rTMS = repetitive transcranial magnetic stimulation

Introduction

The striatum receives two major projections: glutamatergic from most of the cerebral cortex and dopaminergic from the subtantia nigra and ventral tegmental area (Bouyer *et al*., 1984; Sesack and Pickel, 1992). The corticostriatal neurons belong to a series of recurrent parallel loops that project back to the cerebral cortex via the thalamus (Alexander *et al*., 1986). The mesostriatal dopamine neurons, which are also arranged somatotopically, synapse on striatal medium spiny neurons in close proximity to the corticostriatal glutamatergic synapses, upon which they exert a modulatory influence (Bouyer *et al*., 1984; Sesack and Pickel, 1992). Glutamate–dopamine interactions in the striatum play a major role in the normal function of the corticostriatal system, which is involved in a wide range of motor and cognitive functions that includes planning of movement, procedural memory, attention and reward processing. Moreover, abnormalities in glutamate–dopamine interactions are thought to play a role in the pathophysiology of disorders such as Parkinson's disease, schizophrenia and drug addiction (Carlsson and Carlsson, 1990). Two important questions relating to the corticostriato-nigral network in humans are the organization of corticostriatal projections and the way in which the cerebral cortex controls the release of dopamine in the striatum.

Little is known about the anatomical pathways involved in the control of dopamine release in humans. Numerous animal experiments have demonstrated that the frontal cortex exerts an influence on striatal dopamine release, through the modulation of dopamine neuron firing (Karreman and Moghaddam, 1996; Murase *et al*., 1993), but possibly also through a direct effect of corticostriatal

neurons on dopamine nerve terminals. Glutamate, acting locally in the striatum, has been shown to both inhibit and increase dopamine release from nerve terminals, a process that in some cases appears to be independent of dopamine neuron firing (Cheramy *et al*., 1986; Leviel *et al*., 1990). The physiological significance of this phenomenon has been questioned, however, by studies showing that dopamine release only occurs at glutamate concentrations high enough to cause non-physiological effects such as spreading depression.

We recently provided evidence supporting corticostriatal control of dopamine release in humans by using PET and the dopamine receptor ligand [^{11}C]raclopride to measure dopamine release in the striatum following repetitive transcranial magnetic stimulation (rTMS) of the dorsolateral prefrontal cortex (Strafella *et al*., 2001). Dopamine release was only detected focally, in the part of the ipsilateral caudate known to receive most of the projections of the prefrontal area that was stimulated. The most likely explanation for this finding is that rTMS-induced activation of corticostriatal fibres led to focal dopamine release in the projection site of the stimulated cortical area.

In the present study, we sought to confirm this finding by scanning healthy subjects with PET and [^{11}C]raclopride following rTMS of primary motor cortex (M1). Subjects also underwent a control scan following rTMS of the occipital cortex (OCC) on a separate day. There is considerable evidence that *in vivo* binding of benzamide tracers such as [^{11}C]raclopride is inversely proportional to levels of synaptic dopamine at the time of the scan (Dewey *et al*., 1993; Breier *et al*., 1997; Endres *et al*., 1997; Hartvig *et al*., 1997; Laruelle *et al*., 1997; Laruelle, 2000). Statistical parametric maps were generated to detect changes in [^{11}C]raclopride binding between the experimental (M1 rTMS) and control (OCC rTMS) conditions.

Material and methods

Experimental design

Six healthy volunteers (four males, 23–29 years old) participated in the study after giving written informed consent. All subjects were right-handed, and none had a history of neurological or psychiatric illness. Each underwent two [^{11}C]raclopride PET scans (total injected dose 20 mCi), one after rTMS of the left M1 and one after rTMS of a control site, the left OCC. The scan order was randomized across subjects and all the scans were performed at the same time (11.00 am) on two separate days. Autonomic parameters and subjective ratings were collected throughout both test sessions. During the study, the subjects relaxed and kept their eyes closed. Earplugs were used to attenuate the coil-generated clicks. The experiments were approved by the Research Ethics Committee of the Montreal Neurological Institute (MNI) and Hospital.

Location of the target site

To target the same cortical sites in all subjects, a high-resolution MRI 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 (Collins *et al*., 1994). The Talairach coordinates for left finger M1 stimulation ($x = -31$, $y = -22$, $z = 52$) were chosen based on a previous rTMS/PET study (Paus *et al*., 1998). The coordinates for left OCC stimulation ($x = -56$, $y = -58$, $z = -3$) were the same as used previously (Strafella *et al*., 2001). These coordinates were converted into each subject's native MRI space using the reversed native-to-Talairach transformation (Paus *et al*., 1997; Paus, 1999). The positioning of the TMS coil over the MRI-determined locations was performed using the Polaris frameless stereotaxic system (Northern Digital, Waterloo, ON, Canada).

TMS

rTMS was carried out with the Cadwell high-speed magnetic stimulator (Cadwell, Kennewick, WA, USA) using a circular coil with a 9 cm external diameter. Stimulation was performed in the scanner room, with the subject outside the scanner. The coil was held in a fixed position by a mechanical arm over the left M1 or the left OCC. It was positioned so that the anterior tip of the coil was closest to the cortical site, with the rest of the coil tilted away from the skull. Magnetic-induced current under the coil flowed in a posterior–anterior direction. Three rTMS blocks 10 min apart were delivered. Each block consisted of 15 10-pulse trains of 1 s duration (i.e. 10 Hz) with an inter-train interval of 10 s. The stimulation intensity was set at 90% of the resting motor threshold for the right first dorsal interosseous to avoid finger movement during the PET session. The motor threshold, which was determined for each individual prior to the first PET session, was defined as the lowest stimulus intensity able to elicit five motor evoked potentials of at least 50 μV amplitude in a series of 10 stimuli delivered over the left M1 at intervals longer than 5 s. Motor evoked potentials were recorded with Ag/Cl surface electrodes fixed on the skin with a belly-tendon montage. During the PET sessions, subthreshold rTMS over either of the stimulation sites induced no electromyographic responses in the relaxed right first dorsal interosseous nor in the abductor pollicis brevis or extensor digitorum communis.

Subjective ratings and autonomic measures

Electrodermal level, respiration rate and temperature were measured for 2.5 min during a baseline period at the start of the study and during the rest periods following each block of rTMS. After the baseline period and after each rest period, subjects rated their level of comfort, anxiety, fatigue, mood, irritation and pain on a seven-point Likert scale ranging from –3 to 3. For the baseline ratings, subjects were asked to rate how they were currently feeling, while ratings following

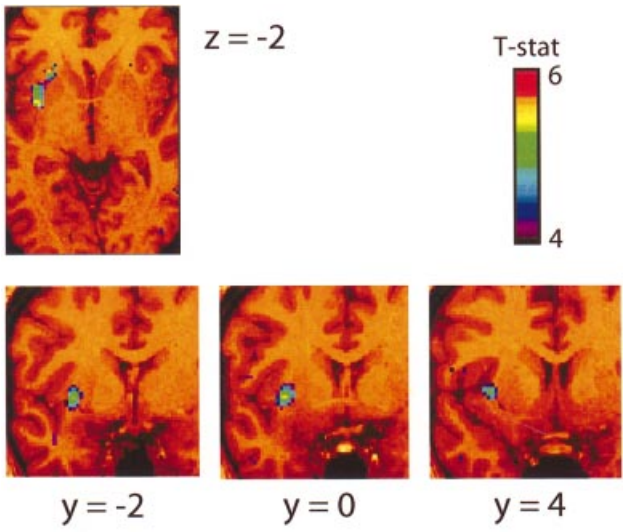

Fig. 1 Dopamine release induced by transcranial magnetic stimulation. One axial and three coronal sections of the statistical parametric map of the change in [^{11}C]raclopride binding potential overlaid on the average MRI of all subjects in stereotaxic space. The colour scale represents the *t*-statistic.

blocks of rTMS referred to how they felt during the preceding rTMS stimulation. The autonomic and behavioural measures were analysed using repeated-measures ANOVA (analysis of variance).

PET

PET scans were obtained with a CTI/Siemens HR+ tomograph operated in three-dimensional mode, yielding images of resolution 4.2 mm full width at half maximum. Within 5 min of the end of the rTMS session, 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 transmission scan was performed with a rotating radioactive source for attenuation correction.

PET frames were summed, registered to the corresponding MRI (Woods *et al*., 1993) and transformed into standardized stereotaxic space (Talairach and Tournoux, 1988) using the transformation parameters previously determined for the MRI, as described above. Thus, coordinates listed in the Results are in Talairach space and correspond to the so-called MNI305 template. Voxel-wise [^{11}C]raclopride binding potential (BP) was calculated using a simplified reference tissue method (Lammertsma and Hume, 1996; Gunn *et al*., 1997) to generate statistical parametric images of change in BP (Aston *et al*., 2000). This method uses the residuals of the least-squares fit of the compartmental model to the data at each voxel to estimate the standard deviation of the BP estimate, thus greatly increasing degrees of freedom. Only peaks falling within the striatum were considered, since this is the only brain structure where receptor-specific [^{11}C]raclopride binding is detected. A threshold level of $t > 4.5$ was considered significant ($P < 0.05$, two-tailed) corrected for multiple comparisons (Worsley *et al*., 1996), assuming a search volume equal to the striatum (estimated conservatively at 72 048 mm^3), an effective image filter of 6 mm full width at half maximum, and 276 degrees of freedom (Aston *et al*., 2000). We determined the search volume by averaging all 12 [^{11}C]raclopride BP maps and counting the number of voxels with mean BP >0.5. We also report cluster sizes, defined here as the area of contiguous voxels with $t > 3.5$ for any peaks meeting the criteria for significance.

Results

rTMS of the left M1 was associated with reduced [^{11}C]raclopride BP in the left putamen compared with rTMS of the left OCC ($t = 5.1$, $P = 0.0001$). The area of decreased [^{11}C]raclopride BP was located in the ventrolateral putamen (Fig. 1), extending in a strip in the anterior–posterior direction. Within this elongated region there were two separate clusters, the largest one having its peak at coordinates $x = –32$, $y = 0$, $z = 0$, extending from $y = –4$ to +7 mm in the anterior–posterior direction (where $y = 0$ mm is the level of the anterior commissure). The peak t was 5.1 and the cluster size was 166 voxels, or 1328 mm^3. A smaller apparently contiguous cluster was located more anterior and ventral in the lateral putamen (peak $t = 5.2$, $x = –24$, $y = 18$, $z = –4$; cluster size, 82 voxels, 656 mm^3). This reduction in [^{11}C]raclopride BP is indicative of an increase in dopamine neurotransmission following cortical stimulation. Table 1 shows BP values from the left and right putamen obtained from regions of interest drawn at the axial level of the statistical peaks. rTMS of the left M1 induced a 9.5% reduction in [^{11}C]raclopride BP in the significant cluster in the left putamen compared with rTMS of the left OCC (mean BP ± SD, OCC rTMS, 2.28 ± 0.69; M1 rTMS, 2.06 ± 0.61). A reduction was present in all six subjects. There was no change in the same region in the right putamen (OCC rTMS, 2.30 ± 0.75; M1 rTMS, 2.30 ± 0.63). The changes in [^{11}C]raclopride BP were not related to the stimulation intensity ($r = 0.1$; not significant). There were no statistically significant differences in any other striatal areas. Statistical analysis of autonomic and behavioural measures revealed no significant main effect of site of stimulation (M1 and OCC) or condition (before and after rTMS), nor any significant site-by-condition interaction (Tables 2 and 3).

Discussion

We have shown that rTMS of the human M1 induces release of dopamine in the ipsilateral putamen, as detected by [^{11}C]raclopride PET. The putamen is the principal input nucleus for somatic motor control in the basal ganglia and receives somatotopically organized corticostriatal projections from the frontal motor areas (Kemp and Powell, 1970; Kunzle, 1975; Jones *et al*., 1977; Liles and Updyke, 1985;

Table 1 *[^{11}C]raclopride binding potential (BP) in the left and right putamen following stimulation of the primary motor cortex and occipital cortex*

Subject	TMS intensity (%)	Left putamen BP			Right putamen BP		
		OCC	M1	%	OCC	M1	%
1	48	1.795	1.558		1.139	1.283	
2	53	2.716	2.516		2.691	2.769	
3	49	1.202	1.142		1.584	1.761	
4	48	3.149	2.749		3.048	2.866	
5	50	2.401	2.093		2.671	2.531	
6	47	2.392	2.301		2.659	2.571	
Mean		2.275	2.059	–9.49	2.298	2.296	–0.07
SD		0.688	0.606		0.753	0.631	

TMS = transcranial magnetic stimulation. TMS intensity is the percentage of the maximum intensity of the apparatus. BP values from the left putamen were extracted from a volume of interest drawn to match the cluster of contiguous voxels with $t > 3.5$ around the statistical peak at $x = –32$, $y = 0$, $z = 0$. These volumes of interest for the left and right putamen were drawn on three adjacent axial sections (centred at $z = 0$) of the subject's MRI in stereotaxic space. The volume of interest for the right putamen was symmetrical to the left putamen volume. OCC = occipital cortex stimulation; M1 = primary motor cortex stimulation.

Table 2 *Mean behavioural ratings before and after repetitive transcranial magnetic stimulation (rTMS) of the motor and occipital cortex*

	Occipital		Motor	
	Baseline	After rTMS	Baseline	After rTMS
Discomfort–comfort	1.25 (1.21)	1.27 (1.27)	1.55 (1.37)	1.67 (1.28)
Anxious–calm	1.70 (1.17)	1.49 (1.24)	1.45 (1.07)	1.44 (1.31)
Fatigued–rested	1.50 (1.55)	1.52 (1.22)	1.50 (1.30)	1.28 (1.48)
Sad–happy	0.83 (0.98)	1.15 (0.61)	1.01 (1.10)	0.93 (1.12)
Irritated–soothed	0.67 (1.13)	1.05 (1.11)	1.00 (1.38)	1.01 (1.12)
Feel pain–do not feel pain	0.54 (0.93)	0.72 (0.98)	0.50 (0.63)	0.69 (1.02)

Seven-point Likert scale ranging from –3 to 3. Numbers in brackets are the standard deviations.

Table 3 *Mean autonomic activity before and after repetitive transcranial magnetic stimulation (rTMS) of the motor and occipital cortex*

	Occipital		Motor	
	Baseline	After rTMS	Baseline	After rTMS
Electrodermal level (μΩ)	5.43 (1.45)	5.34 (1.33)	5.47 (1.40)	5.52 (1.35)
Respiration rate (min^{-1})	16.15 (6.95)	15.94 (5.79)	15.58 (6.02)	15.08 (5.98)
Temperature (°C)	30.49 (7.78)	29.44 (6.37)	29.56 (9.03)	28.46 (8.92)

Numbers in brackets are the standard deviations.

Whitworth *et al*., 1991; Parent and Hazrati, 1995; Inase *et al*., 1996; Takada *et al*., 1998; Tokuno *et al*., 1999). Anterograde tracing studies in monkeys have shown that corticostriatal fibres originating in M1 project to the lateral part of the putamen with a dorsoventral arrangement: the leg represented in the dorsal putamen, the face more ventral, and the arm lying in between these two areas (Kunzle, 1975; Jones *et al*., 1977; Liles and Updyke, 1985; Whitworth *et al*., 1991; Takada *et al*., 1998). The projection areas extend in longitudinal strips in the anterior–posterior dimension. Moreover, in monkeys, there is distal to proximal somatotopy, with the distal forelimb portion of M1 projecting to the most lateral part of the putamen (Tokuno *et al*., 1999). This anatomical location corresponds exactly with the cluster of

dopamine release found in our study following stimulation of the hand area of M1: the lateral part of the putamen with an intermediate location within the dorsalventral plane, extending longitudinally in the anterior–posterior dimension in a strip centred approximately at the level of the anterior commissure (Fig. 1). In the monkey, M1 sends bilateral projections to the putamen (Kunzle, 1975; Jones *et al*., 1977), with the exception of neurons involved in finger movement, whose corticostriatal projections are only ipsilateral (Whitworth *et al*., 1991). This is in accordance with our current finding of dopamine release confined to the ipsilateral putamen following rTMS of the finger representation in M1.

The rTMS-induced release of dopamine in the ipsilateral putamen was most likely the result of activation of corticofugal fibres. Stimuli that are subthreshold for motor responses in relaxed muscle can evoke corticospinal descending volleys (Nakamura *et al*., 1997) and facilitate spinal H reflexes in the absence of any discharge of the spinal motor neurons (Cowan *et al*., 1986; Kujirai *et al*., 1993; Nakamura *et al*., 1997). The finding of reduced [^{11}C]raclopride BP in the known projection area of the stimulated cortical site suggests that dopamine release was mediated by a direct effect of the corticostriatal neurons on striatal dopamine nerve terminals. This confirms the findings of a previous experiment in which we showed that rTMS of the dorsolateral prefrontal cortex was associated with reduced [^{11}C]raclopride binding in its main projection area in the striatum, namely the ipsilateral head of the caudate nucleus (Strafella *et al*., 2001).

Corticostriatal neurons are glutamatergic and synapse on the dendritic spines of medium spiny neurons in close proximity to dopamine nerve terminals located on these same spines (Bouyer *et al*., 1984; Sesack and Pickel, 1992). There is considerable evidence from animal experiments that corticostriatal glutamate can modulate the release of dopamine in the striatum (for reviews, see Whitton, 1997; Morari *et al*., 1998). Electrical stimulation of the frontal cortex causes striatal dopamine release (Nieoullon *et al*., 1978; Taber and Fibiger, 1993). Glutamate directly applied to the striatum promotes local dopamine release, and the effect persists even after the application of tetrodotoxin, implying that dopamine neuron firing is not involved (Cheramy *et al*., 1986; Leviel *et al*., 1990; Keefe *et al*., 1992). Glutamate may be acting on presynaptic dopamine neurons directly (Krebs *et al*., 1991); however, the presence of glutamate receptors on these neurons is controversial (Samuel *et al*., 1990; Whitton, 1997; Morari *et al*., 1998). Another possible mechanism of action involves glutamate-induced release of nitric oxide, which has been shown to promote striatal dopamine release (Hanbauer *et al*., 1992; West *et al*., 2002).

In certain situations, however, striatal glutamate can also inhibit dopamine release, a mode of action that likely involves activation of GABAergic striatonigral neurons leading to inhibition of dopamine neuron firing (Leviel *et al*., 1990; Morari *et al*., 1996; Doherty and Gratton, 1997; Taber and Fibiger, 1997). This suggests that there are different ways for cortex to modulate striatal dopamine release.

Although a direct corticostriatal influence on striatal dopamine terminals most likely accounts for the spatial selectivity of the rTMS effect in our studies, we cannot exclude the involvement of other anatomical pathways. Frontal cortical neurons also project to the substantia nigra (Sesack and Pickel, 1992; Naito and Kita, 1994), where they can modulate the firing of dopamine neurons projecting to the striatum (Murase *et al*., 1993; Karreman and Moghaddam, 1996). However, little is known about the somatotopical organization of this system.

Our finding of spatially restricted dopamine release following cortical stimulation has implications for models of basal ganglia function. One of these models proposes that, during action, 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 centre-surround inhibitory pattern is thought to facilitate this focusing function (Parent and Hazrati, 1993), but dopamine may also play a significant role in this context. There is evidence that dopamine modulates corticostriatal activity by enhancing transmission at active synapses while suppressing it at inactive ones (Wickens and Kotter, 1995) and also by regulating long-term potentiation and depression (Centonze *et al*., 2001). 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 neighbouring ones.

Another conclusion is that dopamine need not only act as a global 'reward' signal. Several models of basal ganglia function are based on animal experiments showing that dopamine neurons fire in a globally homogeneous way in response to rewarding or alerting stimuli (e.g. Schultz, 1998). Our results suggest that, in humans, dopamine may also be released focally in the striatum under the control of cortical areas. This provides evidence for an alternative, more focal, mode of dopamine release than the global response seen in conjunction with rewards.

A limitation of our study is that the parametric image shown in Fig. 1 represents a thresholded statistical map. The area of dopamine release might have been larger than that displayed in the figure. Since PET data are reported so as to limit false-positive results, we cannot be sure that there were not small changes in [^{11}C]raclopride that went undetected by our method. Another limitation relates to the area stimulated by rTMS. While the hand M1 projections were almost certainly stimulated, we cannot exclude the possibility that adjacent cortical areas (premotor and somatosensory cortex) were also stimulated, which may have contributed to dopamine release. However, the premotor corticostriatal projections map to the dorsomedial putamen (Takada *et al*., 1998), where there was no change in tracer binding. The somatosensory corticostriatal projections target the same

areas as M1 in the lateral putamen (Flaherty and Graybiel, 1993).

In summary, we have shown that repetitive stimulation of the cerebral cortex causes dopamine release in the striatal projection of the stimulated area. We conclude that dopamine release may be focally restricted and can be measured using PET. This technique can be applied to the study of glutamate dopamine interactions in health and disease.

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