Theta burst stimulation-induced inhibition of dorsolateral prefrontal cortex reveals hemispheric asymmetry in striatal dopamine release during a set-shifting task – a TMS–^[11C]raclopride PET study

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Abstract

The prefrontostriatal network is considered to play a key role in executive functions. Previous neuroimaging studies have shown that executive processes tested with card-sorting tasks requiring planning and set-shifting [e.g. Montreal-card-sorting-task (MCST)] may engage the dorsolateral prefrontal cortex (DLPFC) while inducing dopamine release in the striatum. However, functional imaging studies can only provide neuronal correlates of cognitive performance and cannot establish a causal relation between observed brain activity and task performance. In order to investigate the contribution of the DLPFC during set-shifting and its effect on the striatal dopaminergic system, we applied continuous theta burst stimulation (cTBS) to left and right DLPFC. Our aim was to transiently disrupt its function and to measure MCST performance and striatal dopamine release during [¹¹C]raclopride PET. A significant hemispheric asymmetry was observed. cTBS of the left DLPFC impaired MCST performance and dopamine release in the ipsilateral caudate–anterior putamen and contralateral caudate nucleus, as compared to cTBS of the vertex (control). These effects appeared to be limited only to left DLPFC stimulation while right DLPFC stimulation did not influence task performance or [¹¹C]raclopride binding potential in the striatum. This is the first study showing that cTBS, by disrupting left prefrontal function, may indirectly affect striatal dopamine neurotransmission during performance of executive tasks. This cTBS-induced regional prefrontal effect and modulation of the frontostriatal network may be important for understanding the contribution of hemisphere laterality and its neural bases with regard to executive functions, as well as for revealing the neurochemical substrate underlying cognitive deficits.

Keywords

basal ganglia; executive function; positron emission tomography; transcranial magnetic stimulation

Introduction

There is clear evidence that damage to the prefrontal cortex impairs performance on cognitive set-shifting tasks (Milner, 1963; Nelson, 1976; Stuss *et al.*, 2000). Functional neuroimaging investigations support these observations (Monchi *et al.*, 2001, 2006b; Owen, 2004). In a previous study, conducted with functional magnetic resonance imaging (fMRI), our group demonstrated differential activation of parts of the prefrontal cortex during performance of a sorting task. In particular, we were able to show that the engagement of the dorsolateral prefrontal cortex (DLPFC) during the provision of feedback after each matching response was consistent with the proposed role of this region in the monitoring of events in working memory (Petrides, 2000; Monchi *et al.*, 2001). From this and other studies it emerged, however, that not only the DLPFC but also the striatum plays a significant role during executive processes requiring planning and set-shifting (Rogers *et al.*, 2000; Monchi *et al.*, 2001, 2004, 2006a, b, 2007; Lewis *et al.*, 2004; Owen, 2004). This co-activation of the DLPFC and the striatum during set-shifting tasks is in line with the well-described cognitive anatomical loop proposed by Alexander *et al.* (1986). In addition, recent positron emission tomography (PET) studies conducted with D2-dopamine receptor ligand [^{11}C]raclopride in healthy subjects while performing the Montreal card-sorting task (MCST; Monchi *et al.*, 2006a) have shown that planning of a set-shift may also be associated with bilateral striatal (i.e. caudate nucleus) reduction in [^{11}C]raclopride binding potential (BP), suggesting that striatal dopamine neurotransmission may increase significantly during the performance of specific executive processes.

Even though functional neuroimaging studies have provided great insights in the role of DLPFC and striatum during set-shifting tasks, neuroimaging alone suffers from the limitation that it provides only neuronal correlates of cognitive performance and often cannot determine a causal relation between observed brain activity and cognitive performance (Rushworth *et al.*, 2002; Johnson *et al.*, 2007). Thus, in the human brain, the specific functional relevance of the DLPFC and striatal dopamine release during set-shifting tasks remains to be established.

Here, we used continuous theta burst stimulation (cTBS), a type of repetitive transcranial magnetic stimulation (rTMS) technique (Huang *et al.*, 2005), to address this issue. We predicted that such application of rTMS to an area of cortex that, at a given time point, is actively involved in processing of task-relevant information would cause performance to decline (Pascual-Leone *et al.*, 1994; Enomoto *et al.*, 2001; Huang *et al.*, 2005) by acting as a 'virtual lesion' (Walsh & Cowey, 2000). In the present study, we tested whether cTBS-induced 'lesioning' of the DLPFC during a set-shifting task would interfere with striatal dopamine release measured with [^{11}C]raclopride PET. D2-dopamine receptor ligand [^{11}C]raclopride 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 rTMS (Strafella *et al.*, 2001, 2003, 2005). To test our hypothesis, we used a computerized sorting task, the MCST, which in our previous fMRI studies showed an engagement of the DLPFC and displayed bilateral release of dopamine in the striatum (i.e. caudate) during [^{11}C]raclopride PET (Monchi *et al.*, 2006a,b, 2007). We hypothesized that if DLPFC–cTBS affects task performance and indirectly interferes with task-induced striatal release of dopamine, an increase in [^{11}C]raclopride BP as compared to the control site would result.

Although it has been previously proposed that the role of the DLPFC resides in monitoring of working memory during the Wisconsin card-sorting task, our group reported some differences between left and right hemisphere. In fact while the right DLPFC was more consistently activated during both positive and negative feedback (monitoring working memory), the left DLPFC was more engaged with processing of negative feedback (set-shifting; Monchi *et al.*, 2001). Greater activation in left DLPFC was also observed in older control subjects during set-shifting with the MCST (Monchi *et al.*, 2007). Other fMRI studies have also pointed out evidence of hemispheric asymmetry in the human lateral prefrontal cortex during cognitive set-shifting (Konishi *et al.*, 2002; Lie *et al.*, 2006). Thus, as hemispheric specialization constitutes an important aspect of executive behavior, we aimed to test such asymmetry. Given the fact that the MCST is designed to have an emphasis on set-shifting compared to other cognitive tasks (i.e. Wisconsin card-sorting task) and based on our previous imaging observations (Monchi *et al.*, 2007) we hypothesized that only the left DLPFC stimulation may interfere with task performance, but not the right DLPFC stimulation.

Materials and methods

Subjects and experimental design

Ten healthy young right-handed adults (20–28 years; four males and six females) participated in the present study after having given written informed consent. They were investigated with [^{11}C]raclopride PET while performing the MCST to measure changes in striatal dopamine release. Each subject underwent three [^{11}C]raclopride PET scans: one after cTBS of the left DLPFC, one following cTBS of the right DLPFC and one after cTBS of the vertex (control site). The scan order was randomized across subjects and scans were performed at the same time on different days. According to the Declaration of Helsinki, the experiments were approved by the Research Ethics Committee of the Centre for Addiction and Mental Health.

TMS protocol

cTBS was carried out with the Magstim Rapid² (Magstim, UK) using a figure-of-eight coil. The coil was held in the scanner in a fixed position by a mechanical arm over the stimulation sites. It was oriented so that the induced electric current flowed under the coil in a posterior–anterior direction. Stimulus intensities, expressed as a percentage of the maximum stimulator output, were set at 80% of the active motor threshold (AMT). AMT was defined

as the lowest stimulus intensity able to elicit five motor evoked potentials (MEPs) of at least 200 μ V averaged over 10 consecutive trials delivered at intervals > 5 s. During the determination of AMT, subjects were instructed to maintain a steady muscle contraction of 20% of maximum voluntary contraction. Audiovisual feedback was given to assist them in maintaining a steady muscle activation (Strafella & Paus, 2000). MEPs were recorded from the contralateral first dorsal interosseus (FDI) muscle with AgCl surface electrodes fixed on the skin with a belly-tendon montage. Electromyogram (EMG) signal was filtered (50 Hz to 50 kHz bandpass) and displayed on the EMGrapher screen (Keypoint, Medtronic, Canada; Strafella *et al.*, 2001). Motor thresholds were measured during the recruitment session and just before PET scans.

Three cTBS blocks (20 s each) were applied to the left and right DLPFC and to the vertex (control site) prior to the MCST (Fig. 1). Successive blocks were separated by 1-min intervals. Each 20-s block consisted of bursts containing three pulses at 50 Hz repeated at 200-ms intervals (i.e. 5 Hz; Huang *et al.*, 2005). In total, 60 s of cTBS (900 pulses) were administered before each PET acquisition scan. This off-line TMS paradigm has two main advantages: it produces a long-lasting (up to 60 min) inhibitory effect limited to the underlying cortex (Di Lazzaro *et al.*, 2005; Huang *et al.*, 2005; Hubl *et al.*, 2008) and it prevents any exogenous influence of the sound and proprioceptive sensation (given by the TMS) during the task performance (Vallesi *et al.*, 2007).

Location of the target site

In order to target the left and right DLPFCs and vertex (control site) we used a procedure that takes advantage of the standardized stereotaxic space of Talairach & Tournoux (1988) and frameless stereotaxy (Paus, 1999; Strafella *et al.*, 2001; Fig. 2). A high-resolution MRI (GE Signa 1.5 T, T1-weighted images, 1 mm slice thickness) of every subject's brain was acquired and transformed into standardized stereotaxic space using the algorithm of Collins *et al.* (1994). The coordinates selected for the left DLPFC ($x = -30$, $y = 40$, $z = 26$) and right DLPFC ($x = 30$, $y = 40$, $z = 26$) were based on previous functional activation studies (Monchi *et al.*, 2006b). The chosen control stimulation site (i.e. vertex region, $x = 0$, $y = -35$, $z = 80$) was based on the lack of activation during performance of the MCST observed in previous studies (Monchi *et al.*, 2001, 2006b) and preliminary TMS-behavioral studies.

The Talairach coordinates were converted into each subject's native MRI space using the reverse native-to-Talairach transformation (Paus, 1999). The positioning of the TMS coil over these locations, marked on the native MRI, was performed with the aid of a frameless stereotaxic system (Rogue Research, Montreal, Canada).

Cognitive task

During the three PET sessions, we used the same set-shifting condition as those of the MCST, i.e. retrieval with shift task (Fig. 3) which, in our previous PET studies, was associated with release of dopamine in the striatum (Monchi *et al.*, 2006a). The task was displayed via a video eyewear (DV920; Icuti Corporation, New York, NY, USA) placed on the plastic thermal mask. In the retrieval with shift task of the MCST (Fig. 3), four reference cards were displayed in a row at the top of the screen in all trials. Blocks of twenty

classification trials (block duration, 4 min; Fig. 1) were preceded by the brief presentation of a single cue card. The cue card did not reappear and had to be remembered throughout the block. 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 dominant right hand. Matching each test card to one of the reference cards was based on a classification rule (color, shape or number) determined by making a comparison between the previously viewed cue card and the current test card (Fig. 3).

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 in each trial. A different cue card was presented before each block. Thirteen blocks separated by 1-min intervals were repeated on a given scanning session (Fig. 1). Subjects underwent a training session of the set-shifting task before the first PET session in order to reduce a possible learning effect.

Positron emission tomography

High resolution PET computational tomography (CT) scans were obtained with a Siemens-Biograph HiRez XVI (Siemens Molecular Imaging, Knoxville, TN, USA) operating in 3-D mode with an in-plane resolution of ~4.6 mm full width at half-maximum. To minimize the subject's head movements in the PET scanner, we used a custom-made thermoplastic facemask together with a head-fixation system (Tru-Scan Imaging, Annapolis, MD, USA). Before each emission scan, following the acquisition of a scout view for accurate positioning of the subject, a low-dose (0.2 mSv) CT scan was acquired and used for attenuation correction.

Within 5 min of the ending of the cTBS session (Fig. 1), 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 28 frames of progressively increasing duration (five 1-min frames, 20 2-min frames, three 5-min frames).

High-resolution MRI (GE Signa 1.5 T, T1-weighted images, 1 mm slice thickness) of each subject's brain was acquired and transformed into standardized stereotaxic space (Talairach & Tournoux, 1988) using automated feature-matching to the MNI template (Collins *et al.*, 1994).

PET frames were summed, registered to the corresponding MRI (Woods *et al.*, 1993) and transformed into standardized stereotaxic space using the transformation parameters previously determined for the MRI. Voxelwise [^{11}C]raclopride BP was calculated using a simplified reference tissue (cerebellum) method (Lammertsma & 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 SD of the BP estimate, thus greatly increasing degrees of freedom. Only peaks falling within the striatum were considered.

A threshold level of $t = 4.0$ was considered significant ($P < 0.05$, two-tailed) corrected for multiple comparisons (Worsley *et al.*, 1996), assuming a search volume equal to the entire

striatum 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.

To confirm our results, two additional analyses (three-way ANOVA and direct contrast) using statistical parametric mapping (SPM2; Wellcome Department of Cognitive Neuroscience, Institute of Neurology) were carried out. For both analyses, averaging over subjects was performed using a random-effects analysis. First, we performed a three-way ANOVA with the factors 'left DLPFC-TMS', 'right DLPFC-TMS' and 'vertex-TMS' (multi-subject PET design with three conditions, F-contrast vector = $[1 \ -1 \ 0; 0 \ 1 \ -1; -1 \ 0 \ 1]^T$). Then, separately, we performed a paired t -test between the conditions 'left DLPFC-TMS' and 'right DLPFC-TMS' (multi-subject PET design, contrast vector = $[1 \ -1]^T$). Parametric images of [^{11}C]raclopride BP transformed into standardized brain space were smoothed with an isotropic Gaussian of 12 mm full width at half-maximum to accommodate intersubject differences in anatomy and enable the application of Gaussian fields to the derived statistical images (Friston *et al.*, 1995). Uncorrected threshold $P < 0.005$ (with extent voxels > 10) was considered significant based on the facts that this analysis was driven by a specific, *a priori*, hypothesis within a small search region (striatum) not involving the whole brain (Friston *et al.*, 1996) and that this was also a confirmatory analysis.

Coordinates listed below are expressed in Talairach space. During the MCST, behavioral responses (i.e. performance time and error trials) were measured. Performance time was calculated from the presentation of the test card to the subject's response, i.e., the selection of a reference card. Error trials were counted as number of incorrect responses. Error trials and performance time of the left and right DLPFC were normalized and expressed as a percentage of the vertex-cTBS-induced behavioral responses (control site). All values are presented as mean $\pm$ SEM.

Results

cTBS of the left DLPFC affected MCST-induced striatal dopamine release resulting in a bilateral increase in [^{11}C]raclopride BP in the striatum as compared to control condition (vertex-cTBS) (Fig. 5). More specifically, [^{11}C]raclopride BP increased by 14.67% (vertex condition, 2.22 ± 0.12 ; DLPFC condition, 2.56 ± 0.20) in the ipsilateral caudate nucleus ($x = -12$, $y = 5$, $z = 15$; $t = 4.6$, cluster size 48 mm^3) and by 12.59% (vertex condition, 2.50 ± 0.08 ; DLPFC condition, 2.80 ± 0.10) in the contralateral caudate ($x = 18$, $y = 8$, $z = 14$; $t = 4.8$, cluster size 40 mm^3 ; Figs 4 and 5). A significant area of change in [^{11}C]raclopride binding was also observed in the ipsilateral putamen, 12.98% (vertex condition, 3.29 ± 0.13 ; DLPFC condition, 3.69 ± 0.18) with its peak ($t = 4.6$) at coordinates $x = -21$, $y = 6$, $z = 3$. No changes in BP were detected in the contralateral putamen or anywhere in the ventral part of the striatum.

While cTBS of the left DLPFC interfered with the MCST-induced striatal dopamine release, cTBS of the right DLPFC did not affect MCST-induced dopamine release and did not induce any changes in striatal [^{11}C]raclopride BP as compared to the control condition (vertex-cTBS).

Additional analysis using SPM2 confirmed our results. Three-way ANOVA (left DLPFC, right DLPFC and vertex stimulation) showed a significant effect on BP in the left and right caudate nucleus and left putamen ($F_{2,18} > 3.5$, $P < 0.005$ uncorrected, extent threshold > 10 voxels). A direct contrast of the left vs. right DLPFC stimulation revealed a greater [^{11}C]raclopride BP (i.e. reduced task-related dopamine release) in the bilateral caudate nucleus and left putamen ($t_9 > 2.5$, $P < 0.001$ uncorrected, extent threshold > 10 voxels; Fig. 6).

Behaviorally, cTBS of the left DLPFC induced an increase of $75.38 \pm 44.18\%$ in error trials during the MCST as compared to the right DLPFC–cTBS (error trials, $-3.95 \pm 18.03\%$; paired t -test, $t_9 = 2.264$; $P < 0.05$; Fig. 7). A direct comparison between left and right DLPFC–cTBS-induced error trials confirmed the significant difference (paired t -test $t_9 = 2.383$; $P < 0.05$). Performance time, however, was not affected by either left ($0.75 \pm 4.78\%$) or right ($-4.37 \pm 5.03\%$) DLPFC stimulation (paired t -test, $t_9 = 1.665$; $P > 0.05$).

Discussion

In the present study, cTBS of the left DLPFC affected MCST performance and resulted in interference upon dopamine release in the ipsilateral caudate–anterior putamen and contralateral caudate nucleus, as compared to cTBS of the control site (i.e. vertex). These effects appeared to be limited to the left DLPFC stimulation while cTBS of the right DLPFC did not impair task performance and did not influence [^{11}C]raclopride BP anywhere in the ipsilateral and/or contralateral striatum (as compared to control site; Figs 4, 5 and 7).

Subthreshold cTBS of the frontal cortex is believed to produce a long-lasting inhibition (up to 60 min) of the underlying cortex (Huang *et al.*, 2005; Nyffeler *et al.*, 2006; Vallesi *et al.*, 2007) and seem to involve plasticity-like changes at the synaptic connections, possibly mediated by NMDA receptors (Huang *et al.*, 2007). These observations have been confirmed both with neurophysiological studies (Di Lazzaro *et al.*, 2005) and more recently with fMRI investigations (Hubl *et al.*, 2008). The latter has demonstrated that cTBS of the frontal eye field is responsible for a long-lasting decrease in the task-related BOLD response recovering to a pre-stimulation level ~60 min after stimulation. Based on these reports and according to our predictions, cTBS affected DLPFC activity and indirectly interfered with the task-induced striatal release of dopamine (Monchi *et al.*, 2006a), resulting in an increase in [^{11}C]raclopride BP (as compared to the control site stimulation).

These findings confirm and further extend our previous observations that set-shifting tasks, such as the MCST, while engaging DLPFC may also influence dopamine release in the striatum (Monchi *et al.*, 2006a, b, 2007).

These observations are in keeping with several reports. In fact, while it is well known that damage to the prefrontal cortex impairs performance on set-shifting tasks (Milner, 1963; Nelson, 1976; Stuss *et al.*, 2000), other studies of dopamine depletion in non-human primates have proposed a possible involvement of striatal dopamine in set-shifting tasks (Roberts *et al.*, 1994; Collins *et al.*, 2000). Similarly, neuroimaging studies have demonstrated that changes in striatal dopamine levels can modulate certain cognitive

processes and that the level of cognitive impairment may depend on the level of dopamine depletion (Cropley *et al.*, 2006). Consistent with this hypothesis, PET studies performed in patients with Parkinson's disease and healthy subjects following tyrosine- and phenylalanine-induced depletion (Marie *et al.*, 1999; Lozza *et al.*, 2004; Owen, 2004) have shown a significant correlation between executive task performances and striatal dopamine denervation.

In support of our working hypothesis, particularly intriguing was the observation that only left and not right DLPFC stimulation-induced interference was responsible for the observed results in these right-handed young healthy subjects (Figs 4–7). This is consistent with previous lesion studies. The impaired top-down control of task-set reconfiguration has been reported to be involved with left frontal lesion while right frontal lesion has been associated with inhibition of inappropriate responses (Rogers *et al.*, 1998; Aron *et al.*, 2004). Stuss & Alexander (2007) argued in their extensive review of frontal lesions and executive function that task-setting processes are consistently impaired after damage to the left prefrontal cortex. This task setting–left frontal relationship has also been observed during the Wisconsin card-sorting task in relation to set-loss errors. Other lesion studies have attempted to identify regional frontal effects using the Stroop task and have defined underlying impaired neural mechanisms supporting, in general, the assumption that left prefrontal cortex lesions affect setting of stimulus–response contingencies (Richer *et al.*, 1993). More recently, fMRI studies using variations of the standard Stroop paradigm and Wisconsin card-sorting task have also supported these observations and confirmed hemispheric asymmetry in DLPFC during cognitive tasks (Derrfuss *et al.*, 2005). Specific regional prefrontal effects as consequence of cTBS have also been observed in other recent studies (Vallesi *et al.*, 2007), where these authors while testing different cognitive processes such as implicit temporal processing (e.g. foreperiod effect) have provided evidence of a specific contribution of, this time, the right (but not left) DLPFC.

cTBS-induced changes in BP were observed in both the caudate and anterior putamen (Figs 5 and 6), in accordance with anatomical (Alexander *et al.*, 1986) and functional (Monchi *et al.*, 2001, 2006a, b) imaging studies. In rhesus monkeys 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 previous fMRI studies, we reported co-activation of the prefrontal cortex with the caudate nucleus and putamen, respectively, during planning and execution of a set-shift (Monchi *et al.*, 2001, 2006b). Other imaging studies conducted in Parkinson's disease patients have also revealed a significant correlations between executive processes and dopamine transporter densities in the caudate and putamen (Muller *et al.*, 2000). A similar relationship between executive functioning and [18F]fluorodopa uptake in the putamen has been observed in more recent PET studies (van Beilen & Leenders, 2006). Traditionally, the putamen, unlike the caudate nucleus, has always been associated with motor-related activities rather than with cognitive functions. However, there is clear evidence that the role of the putamen may be linked not directly to the movement itself but rather to the condition under which it is made (Tolkunov *et al.*, 1998).

Left cTBS of the DLPFC affected release of dopamine in bilateral caudate nucleus (Figs 5 and 6). This TMS-induced prefrontal–striatal network modulation is consistent with the bilateral involvement of striatal dopaminergic function in relation to a working memory task recently been documented by Landau *et al.* (2008). These results confirmed our previous PET study (Monchi *et al.*, 2006a) which showed changes in [^{11}C]raclopride BP during the same set-shifting condition in the left and right caudate nucleus. Thus, assuming that this behavioral task engages both caudate nuclei, it follows that cTBS-induced interference with the task affects both caudate nuclei similarly. In the context of a prefrontal–striatal network modulation induced by TMS, however, it is important to keep in mind that TMS may influence neural activity both locally in the tissue under the coil and remotely to the stimulation site, presumably through trans-synaptic connections (Pascual-Leone *et al.*, 2000; Walsh & Cowey, 2000; Strafella *et al.*, 2001).

Our study provides indirect evidence of frontostriatal modulation of striatal dopamine during the performance of set-shifting processes. To our knowledge, this is the first study showing that rTMS may indirectly affect task-induced striatal dopamine neurotransmission by disrupting left prefrontal function while involved in processing task-relevant information. This rTMS-induced regional prefrontal inhibition and its modulation of the frontostriatal network may be important for understanding the contribution of hemisphere laterality and the neural bases of executive functions such as planning and set-shifting. It may also help identify the neurochemical substrate underlying deficits in cognitive functions observed in neurological disorders associated with dopamine dysfunction, such as Parkinson's disease.

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Abbreviations

AMT	active motor threshold
BP	binding potential
CT	computational tomography
cTBS	continuous theta burst stimulation
DLPFC	dorsolateral prefrontal cortex
FDI	first dorsal interosseus
fMRI	functional MRI
MCST	Montreal card-sorting task
MEP	motor evoked potential
MRI	magnetic resonance imaging
PET	positron emission tomography

rTMS	repetitive transcranial magnetic stimulation
SPM	statistical parametric mapping

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Fig. 1.

Timeline of the experimental setup. All subjects went through three [¹¹C]raclopride PET scans on different days at the same time. On each day, the TMS coil was positioned on either the left DLPFC, the right DLPFC or the vertex (control site). Three cTBS blocks (20 s each) were applied prior to the MCST. Successive blocks were separated by 1-min intervals. Each 20-s block consisted of bursts containing three pulses at 50 Hz repeated at 200-ms intervals (i.e. at 5 Hz). In total, 60 s of cTBS (900 pulses) were administered for each PET session. Participants started the MCST after the cTBS sessions and continued until the end of the PET scan. The [¹¹C]raclopride was injected within 5 min following cTBS. Thirteen 4-min blocks separated by 1-min intervals were repeated on a given scanning session.

Fig. 2.

The TMS coil was located over (a) the left DLPFC ($x = -30$, $y = 40$, $z = 26$), (b) the right DLPFC ($x = 30$, $y = 40$, $z = 26$) or (c) the vertex (control site; $x = 0$, $y = -35$, $z = 80$). The positioning of the TMS coil over these locations, marked on the native MRI, was performed with the aid of a frameless stereotaxic system.

Fig. 3.

Montreal card-sorting task. A cue card appears for 3.5 s at the beginning of a block of twenty classification trials. A different cue card was presented before each block. In this example, the cue card contains three red stars. After the cue card disappears, four reference cards were displayed in a row at the top of the 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 based on a classification rule (color, shape or number) that is determined by making a comparison between the previously viewed cue card and the current test card. 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 in each trial.

Fig. 4.

In the lower panel [^{11}C]raclopride binding potential (mean $\pm$ SE) during MCST performance after left DLPFC stimulation and vertex stimulation (control), from left caudate ($P < 0.05$), right caudate ($P < 0.05$) and left putamen ($P < 0.05$), extracted from a spherical region of interest centered at the x , y and z coordinates of the statistical peak revealed by the parametric map. In the upper panel the solid dots represent individual BPs.

Fig. 5.

(a) Comparison between left DLPFC and vertex stimulation (control condition). Sagittal ($x = -12$ and $x = -22$) and axial ($z = 14$) 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 changes during MCST performance after left DLPFC stimulation compared to vertex stimulation (control). (b) Comparison between right DLPFC and vertex stimulation showing the lack of changes in [^{11}C]raclopride BP.

Fig. 6.

Direct contrast of the left vs. right DLPFC stimulation showed higher BP (i.e. reduced task-related dopamine release) in the bilateral caudate nucleus ($z = 12$) and left putamen ($x = -28$; $t_9 > 2.5$, $P < 0.001$ uncorrected, extent threshold > 10 voxels).

Fig. 7.

In the lower part of the figure, DLPFC–cTBS-induced error trials during the MCST are expressed as a percentage of the error trials of the vertex–cTBS (control site). Left DLPFC increased error trials by $75.38 \pm 44.18\%$ as compared to right DLPFC–cTBS, which did not affect task performance (error trials, $-3.95 \pm 18.03\%$; paired *t*-test, $t_9 = 2.264$; $P < 0.05$). Error bars indicate SEM. The upper part of the figure shows individual numbers of errors during the MCST after cTBS.