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Review Article

PET functional imaging of deep brain stimulation in movement disorders and psychiatry

Benedicte Ballanger^{1,2}, Marjan Jahanshahi³, Emmanuel Broussolle^{2,4} and Stéphane Thobois^{2,4}

¹PET Imaging Centre, Center of Addiction Mental Health, University of Toronto, Toronto, Ontario, Canada;

²CNRS, UMR 5229, Institut des Neurosciences Cognitives, Lyon, France; ³Sobell Department of Motor Neuroscience and Movement Disorders, Institute of Neurology, London, UK; ⁴Université Lyon I, Hospices Civils de Lyon, Hôpital Neurologique Pierre Wertheimer, Lyon, France

Deep brain stimulation (DBS) represents a major advance in the treatment of various severe movement disorders or neuropsychiatric diseases. Our understanding of the mechanism of action of this surgical treatment has greatly benefited from functional imaging studies. Most of these studies have been conducted in patients with Parkinson's disease (PD) treated by bilateral subthalamic nucleus (STN) stimulation. These studies have notably underlined the fact that STN stimulation influences motor, limbic, or associative cortical-subcortical loops in various (sometimes contradictory) ways. We present an up-to-date review of the information provided by functional imaging studies in surgery for PD, dystonia, tremor, as well as in psychiatric disorders such as depression or obsessive-compulsive disorder. On the basis of this information, proposed mechanisms of action of DBS are discussed, as well as the need for additional approaches such as improved anatomical localization of the contact used for stimulation or a better understanding of the electrical distribution around the electrode.

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Keywords: deep brain stimulation; movement disorders; PET; psychiatry

Introduction

During the past two decades, deep brain stimulation (DBS) has been recognized as an efficient therapy for tremor (target = thalamus), Parkinson's disease (PD) (targets = subthalamic nucleus (STN), or internal segment of the globus pallidus (GPi), thalamus, pedunculo-pontine nucleus (PPN)), and dystonia (target = GPi) (Benabid *et al.*, 1993; Coubes *et al.*, 2000; Limousin *et al.*, 1995). The indications are growing rapidly and recent reports suggest its efficacy in Gilles de la Tourette syndrome, depression, and obsessive-compulsive disorder (OCD) (Aouizerate *et al.*, 2005; Houeto *et al.*, 2005; Mallet *et al.*, 2008; Mayberg *et al.*, 2005). However, despite its effectiveness, its mechanisms of action remain a matter of debate (Benazzouz and Hallett, 2000; Kringsbach *et al.*, 2007; McIntyre *et al.*, 2004; Vitek, 2002). Functional imaging using positron emission

tomography (PET) or single-photon emission computed tomography (SPECT) provides a direct *in vivo* approach to fill this gap in our knowledge. The aim of this review was to summarize the contributions that have been made by functional imaging in the understanding of DBS in different disorders and to consider the directions that future imaging studies of DBS may take.

Materials and methods

Data for this review were identified by searches on Medline using the terms 'deep brain stimulation', 'thalamus', 'subthalamic nucleus', 'internal pallidum', 'Parkinson', 'tremor', 'dystonia', 'obsessive compulsive disorders', 'Tourette syndrome', 'depression', 'functional imaging', 'PET', and 'SPECT'. References were also identified from relevant articles and through searches of the author's files. Only papers published in English were reviewed.

Correspondence: Dr S Thobois, Hôpital Neurologique Pierre Wertheimer, Neurologie C, 59 Bd Pinel, Bron 69677, France.

E-mail: stephane.thobois@chu-lyon.fr

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Summary of the Different Radiotracers Used

Positron emission tomography and more rarely SPECT are classically used to better understand the mechanism of

action and consequences of DBS. Functional magnetic resonance imaging (MRI) is not performed in DBS-implanted patients for safety reasons. Several PET radiotracers can be used. $H_2^{15}O$ explores the changes in cerebral blood flow induced by stimulation during a specific task. The dopaminergic function can be analyzed using ^{18}F -Dopa, a presynaptic dopaminergic tracer, and [^{11}C]-raclopride, a dopamine D2 receptor ligand, the binding of which is dependent on the amount of endogenous extracellular dopamine. In addition, several radiotracers have been developed for monitoring the integrity of the presynaptic dopaminergic system affected in PD based on DAT antagonists such as methylphenidate and cocaine (tropane derivatives) (Shih *et al*, 2006). By labeling glucose (^{18}F -fluorodeoxyglucose, FDG), the radiotracer imaging technique can determine local metabolism.

Summary of the Model of Basal Ganglia Circuitry

Before considering functional imaging studies of DBS in different diseases, it is useful to give a brief and simplified overview of the organization of basal ganglia (BG) circuitry. Cortico-basal ganglia-cortical circuits are organized in parallel, largely segregated but interconnected, closed-loop projections (Alexander *et al*, 1986). These circuits can be divided into motor (putamen projecting mostly to the supplementary motor area (SMA), motor cortex, and the lateral premotor area), associative (dorsal caudate projecting to the dorsolateral prefrontal cortex (DLPFC)), and limbic loops (ventral striatum projecting mostly to the anterior cingulate cortex (ACC) and orbital frontal cortex; Figure 1). In each nucleus of the BG, motor, associative and limbic territories are represented (Alexander *et al*, 1986). This is crucial while analyzing the effect of DBS, notably STN DBS, during motor, cognitive, or emotional tasks.

The PD model of bradykinesia has been developed from research conducted in a parkinsonian monkey in the late 1980s, and has then been progressively modified to become

considerably more complex (DeLong, 1990; Yelnik, 2008). Although oversimplified, this model may help us understand or predict the changes of brain activation induced by DBS, especially in PD. Briefly, the cortex sends projections to the striatum. The striatum projects to the GPi through two different pathways: a direct striatal-pallidal pathway, which facilitates movement, and an indirect striatal-GPe-STN-GPi pathway, which inhibits movement. Both pathways receive dopaminergic innervation from the substantia nigra pars compacta (SNc), providing an inhibition of the excitatory indirect pathway and an excitation of the inhibitory direct pathway. The GPi, PPN, and substantia nigra pars reticulata (SNr) receive excitatory projections from STN. GPi, the main output area of BG, sends inhibitory projections to the thalamus, which in turn projects to the cortex (Figure 2A). In PD, the dopaminergic degeneration in SNc leads to a profound dysfunction of these pathways, with a hyperactivity of the indirect pathway and a reduction in activity of the direct pathway. In PD STN, neuronal activity is increased, which induces an inhibition of the thalamus through the GPi and, in turn, a reduction in thalamocortical excitatory input (Figure 2B). According to this model, STN DBS, which is supposed to be inhibitory, or subthalamotomy should reduce the overactivity of STN and reverse the inhibitory output from the GPi to the thalamus and, in turn, improve cortical activation (Figure 2C). In dystonia, dysfunction is even more complex and both the indirect and direct pathways are hyperactive, leading to an abnormal pattern of GPi activity that reduces its inhibition of the thalamus and subsequently induces a release of thalamocortical activity (Vitek *et al*, 1999).

Functional Imaging Studies in Parkinson's Disease

Effect of DBS at rest: Subthalamic nucleus stimulation has been developed in the early 1990s to alleviate severe motor symptoms in PD (Limousin *et al*, 1995). This treatment improves all components of the parkinsonian triad, as well as levodopa-induced motor complications, and allows a major reduction in medication intake in patients with advanced PD (Kleiner-Fisman *et al*, 2006).

In the resting state, network analyses of ^{18}F -FDG PET data have reported the presence of an abnormal spatial covariance pattern associated with the motoric features of PD (Eckert *et al*, 2007; Eidelberg *et al*, 1994; Moeller *et al*, 1999). This PD-related covariance pattern is characterized by increased pallidal, thalamic, and motor cortical metabolic activities associated with relative reductions in the lateral premotor cortex and the parieto-occipital regions (Eidelberg *et al*, 1994). A reduced expression of this abnormal PD-related covariance pattern has been observed during STN DBS (Trost *et al*, 2006), as well as during GPi DBS (Fukuda *et al*, 2001b). Interestingly, direct comparisons between STN DBS and dopaminergic medication have been carried out, which showed no difference in the degree of PD-related covariance pattern modulation (Asanuma *et al*, 2006; Hirano *et al*, 2008), supporting a common mechanism for these therapies (Krack *et al*, 2002; Vingerhoets *et al*, 2002).

Parallel cortical-basal ganglia-cortical circuits

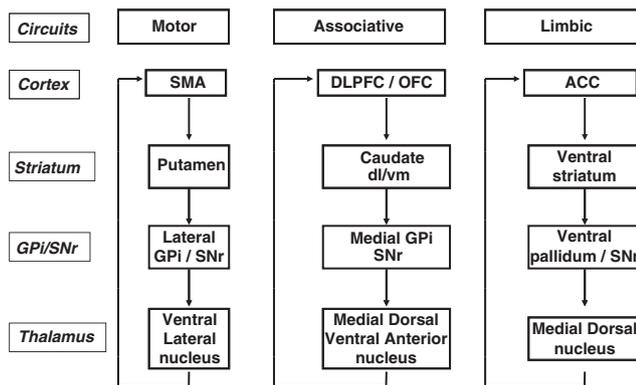


Figure 1 Parallel loop models of corticostriatal connectivity. SMA, supplementary motor area; DLPFC, dorsolateral prefrontal cortex; ACC, anterior cingulate cortex; GPi, internal globus pallidus; SNr, substantia nigra pars reticulata; VL, ventrolateral; VA, ventroanterior; DM, dorsomedial.

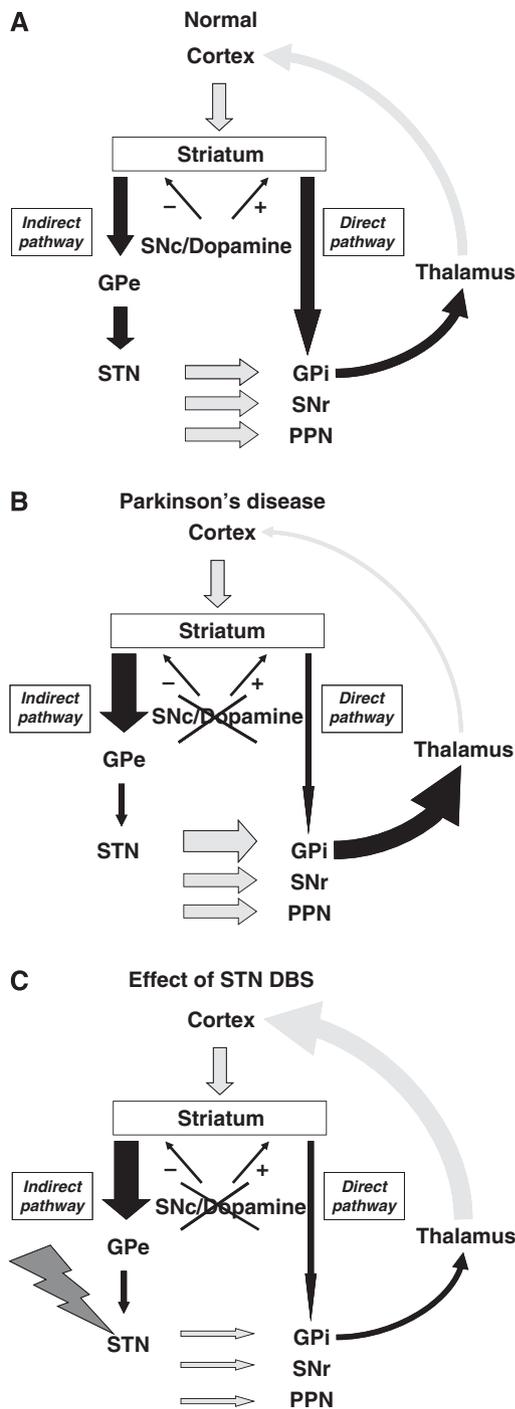


Figure 2 Cortical-subcortical loops in (A), normal subjects; (B), Parkinson's disease; (C), consequences of STN stimulation. Gray arrows, glutamatergic pathway; black arrows, GABAergic pathway. SNc, substantia nigra pars compacta; STN, subthalamic nucleus; GPi, internal globus pallidus; GPe, external globus pallidus; SNr, substantia nigra pars reticulata; PPN, pedunculopontine nucleus.

Overall, a decrease in abnormal motor and cerebellar activities has been consistently reported with STN stimulation (Asanuma *et al*, 2006; Geday *et al*, 2009; Hershey *et al*, 2003; Trost *et al*, 2006). This decrease observed in the

motor cortex was found to be proportional to the frequency of stimulation (Haslinger *et al*, 2005) and was associated with clinical improvements (Cilia *et al*, 2009). In addition, a significant correlation between improvement of rigidity and decreased regional cerebral blood flow (rCBF) in the SMA has recently been observed (Karimi *et al*, 2008). In contrast, STN DBS has been found to increase activity in precuneus and occipitotemporal cortices (Asanuma *et al*, 2006; Cilia *et al*, 2009; Geday *et al*, 2009; Goerendt *et al*, 2006; Grafton *et al*, 2006), consistent with the known preferential activation of these areas during resting states (Raichle *et al*, 2001). These results indicate that this rest-related activation is impaired in PD and restored by STN DBS.

With respect to subcortical structures, the literature is more equivocal. Indeed, metabolic studies using PET and ^{18}F -FDG in resting PD patients have shown that STN DBS reduces glucose metabolism in the putamen and GPi (Asanuma *et al*, 2006; Trost *et al*, 2006). However, recent data suggested that STN DBS acts at rest through an excitatory mechanism with activation of the STN and the directly connected GPi (Geday *et al*, 2009; Hilker *et al*, 2008). Furthermore, although some studies reported increased activity in the thalamus during STN DBS (Goerendt *et al*, 2006; Hershey *et al*, 2003; Hilker *et al*, 2004; Karimi *et al*, 2008), others observed decreased activity (Geday *et al*, 2009). Altogether, these data are difficult to reconcile with a simple model of STN inhibition (which would only lead to an increase in cortical activation) or excitation (which would only, according to the BG model, lead to a decrease in cortical activation). Electrophysiological studies have also shown opposite findings, some showing that STN DBS induces an increase in GPi neuronal activity (in favor of an excitatory mechanism) and others finding a decrease in GPi and an increase in thalamic electrophysiological activity (in favor of an inhibitory mechanism) (Benazzouz and Hallett, 2000; Windels *et al*, 2000). It is noteworthy that methodological differences may account for some of the discrepancies (Geday *et al*, 2009). In keeping with this idea, it has recently been suggested, for instance, that increases in subcortical regions are an artifactual by-product of biased ratio normalization to the global mean used in studies comparing PD patients with healthy subjects (Borghammer *et al*, 2009).

Effect of DBS during motor execution: In PD, bradykinesia and rigidity have been shown to be related to a lack of activation of the DLPFC, SMA, and ACC because of an inhibition of the thalamocortical excitatory pathway (Jahanshahi *et al*, 1995; Jenkins *et al*, 1992; Playford *et al*, 1992). In parallel, the recruitment, even at an early stage of the disease, of 'accessory' pathways or regions has been recognized in numerous studies (Rascol *et al*, 1997; Sabatini *et al*, 2000; Samuel *et al*, 1997; Thobois *et al*, 2000). These overactivations could either correspond to a positive phenomenon (i.e., leading to the improvement of motor performance) or only reflect the inability of the central nervous system to select the appropriate program to perform the task (Hanakawa *et al*, 1999; Turner *et al*, 2003; Yu *et al*, 2007).

Functional imaging studies using $H_2^{15}O$ PET have shown that, during motor execution, DBS of the STN induces an increased activation of the DLPFC, SMA, and ACC and, concomitantly, a decreased activation of the so-called 'accessory' pathways (Ceballos-Baumann *et al*, 1999; Grafton *et al*, 2006; Hershey *et al*, 2003; Limousin *et al*, 1997; Strafella *et al*, 2003a; Thobois *et al*, 2002). Interestingly, most of these studies are consistent with clear task-dependent changes of brain perfusion induced by STN DBS. In addition, it has been argued that during motor execution, STN DBS selectively improves the recruitment of appropriate motor areas and suppresses the activation of inappropriate or competing cortical regions, whereas in resting PD patients, the effect of STN stimulation is a reduction of an abnormally high activity in the motor cortex (Ceballos-Baumann *et al*, 1999; Geday *et al*, 2009; Payoux *et al*, 2004).

The neural correlates of GPi stimulation in PD have been less investigated. Two studies have found an increase in ACC and SMA activation during motor execution similar to what is observed after STN DBS (Fukuda *et al*, 2001a; Limousin *et al*, 1997). In contrast, no increase in DLPFC activation was observed, which constitutes a major difference from STN DBS and could be explained by differential pathways influenced by stimulating each target.

Effect of DBS of the PPN on gait-related symptoms of PD: The PPN region is involved in gait initiation and maintenance (Pahapill and Lozano, 2000). In advanced PD, gait and postural instability become a major issue for clinical management, as they are usually resistant to levodopa and STN DBS. In animal model of PD, the electrophysiological activity of PPN is reduced and stimulation or disinhibition of this structure can improve gait and akinesia (Jenkinson *et al*, 2004). Recently, some studies have shown that PPN DBS at a low frequency can improve gait disturbance and freezing in advanced PD (Stefani *et al*, 2007). At present, however, the mechanism of action of PPN DBS remains unclear. To date, only two PET activation studies have been reported, showing that (1) at rest, unilateral PPN DBS increases rCBF bilaterally in the thalamus and ipsilaterally to the stimulation in the putamen, cerebellum, and insular cortex in an advanced PD patient (Strafella *et al*, 2008); and (2) during a self-paced alternating motor task of the lower limbs, unilateral PPN DBS increases rCBF in the medial sensorimotor areas (including caudal SMA) in three advanced PD patients (Ballanger *et al*, 2009). Interestingly, this latter observation was associated with changes in the lower limb movement pattern represented by a lower frequency and an increase in amplitude. This indicates that PPN DBS may induce significant functional changes in the neural networks associated with the control of voluntary movements of the lower limbs. However, whether these findings account for the proposed clinical effects of DBS PPN remains to be proven in a larger sample of patients.

Effect of DBS during speech: Dysarthria is a disabling symptom frequently encountered in advanced PD. In healthy subjects, speech production is associated with a

bilateral activation of the orolingual region of the primary motor cortex and of the cerebellum, thalamus, and caudate (Murphy *et al*, 1997). In PD, the profile of brain activation impairment during speech is different from the one reported during limb movements. Indeed, the primary motor cortex and cerebellum are underactivated, whereas SMA and DLPFC are overactivated during speech in PD patients relative to healthy controls (Pinto *et al*, 2004). These overactivations may correspond to compensatory mechanisms or may alternatively contribute directly to the pathophysiology of dysarthria. STN DBS does not usually improve speech intelligibility, but several studies have reported an improvement in some phonatory and articulatory speech parameters in patients with PD (Gentil *et al*, 2001). In PD patients with a clear improvement in the biomechanical components of speech induced by STN DBS, a PET activation study revealed that this improvement was associated with a correction of abnormalities of the brain activation profile described above (Pinto *et al*, 2004). Indeed, an increased activation of the primary motor cortex and cerebellum and a decreased activation of SMA were shown. This study also shows that the consequences of STN DBS are clearly task dependent and mostly consist of restoring a selective pattern of brain activation and suppressing inappropriate cortical recruitment.

Effect of DBS on cognition: Overall, STN stimulation does not lead to cognitive deterioration in carefully selected patients (Castelli *et al*, 2006; Witt *et al*, 2008). However, concerns have been raised by reports of changes in specific aspects of cognition (Krack *et al*, 2003). Of these, an impairment of specific cognitive tasks that require response selection through an inhibition of inappropriate or competing responses has repeatedly been reported (Ardouin *et al*, 1999; Jahanshahi *et al*, 2000a; Saint-Cyr *et al*, 2000). These response conflict tasks represented, for example, by Stroop and random number generation (RNG) are mostly mediated by ACC or the prefrontal cortex (Carter and van Veen, 2007; Jahanshahi *et al*, 2000b). Positron emission tomography studies comparing 'on' versus 'off' stimulation conditions in PD have shown that DBS of the STN is associated with decreased rCBF in the ACC and ventral striatum during Stroop and with decreased rCBF in the right orbitofrontal cortex, the left inferior frontal gyrus, and the left inferior temporal gyrus during a verbal fluency task (Schroeder *et al*, 2002, 2003). Random number generation is another example of a task, in which the participant has to generate numbers between 1 and 9 in a random manner that requires suppression/avoidance of habitual counting in series. During RNG, DLPFC and ACC are significantly activated relative to a control counting task, and rCBF in the left DLPFC is negatively associated with a measure of habitual counting during RNG and with rCBF in the temporal cortex (Jahanshahi *et al*, 2000b). It has been proposed that during RNG, strategic response selection and generation of numbers in a random manner is achieved through the inhibitory influence of the left DLPFC over the superior temporal cortex, the putative site of a number associative network, to keep activity in this area low and to prevent spreading activation in the

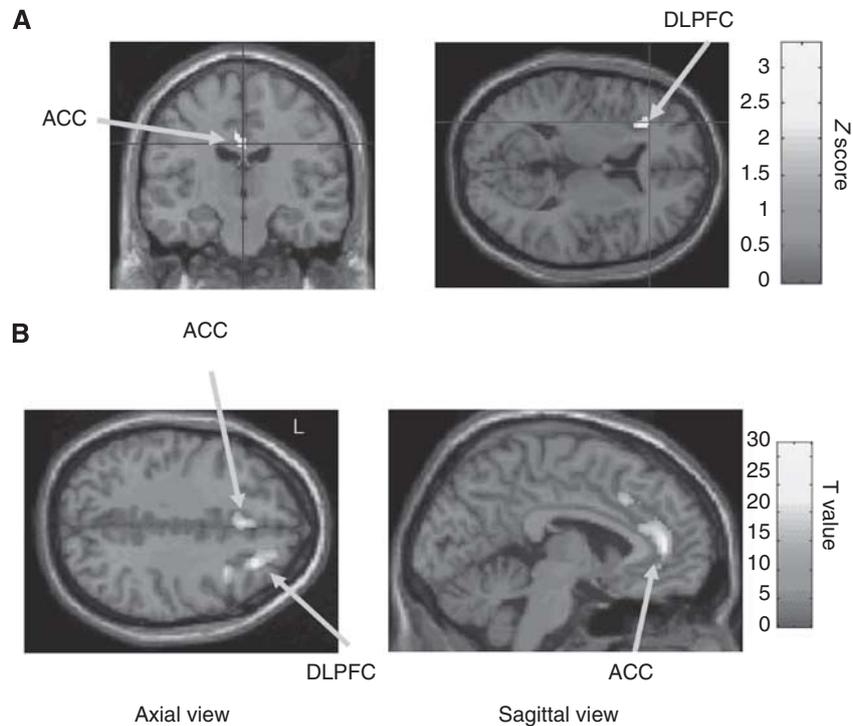


Figure 3 (A) Areas of decreased activation induced by STN stimulation during random number generation in a group of patients with Parkinson's disease. PET H₂¹⁵O study. Data are superimposed on transverse sections of a single-subject brain MRI from SPM 99. (B) Areas of increased activation during hypomanic state induced by STN stimulation in a single patient. PET H₂¹⁵O study. Data are superimposed on axial and sagittal sections of a single-subject brain MRI from SPM 2. ACC, anterior cingulate cortex; DLPFC, dorsolateral prefrontal cortex.

network. With DBS of the STN, performance of PD patients on fast-paced RNG is worse on 'on' stimulation compared with 'off' stimulation. This is because of increased rCBF in the GPi and decreased rCBF in the left DLPFC and in the anterior and posterior cingulate cortex (Thobois *et al*, 2007). The impaired performance induced by STN DBS on verbal fluency, the Stroop, and fast-paced RNG has been related to a reduced activation of DLPFC and ACC, two areas involved in response selection through an inhibition of inappropriate or competing responses (Figure 3A; Thobois *et al*, 2007). In keeping with these observations, a significant linear relationship between glucose uptake and verbal fluency performance after STN DBS in advanced PD patients has recently been observed (Kalbe *et al*, 2009). The best correlations were found in the frontal lobe, including the left DLPFC and Broca area, as well as in the right dorsal ACC. Thus, in PD, DBS of the STN can improve the functioning of circuits involved in motor execution (Ceballos-Baumann *et al*, 1999; Grafton *et al*, 2006; Limousin *et al*, 1997; Strafella *et al*, 2003a; Thobois *et al*, 2002) and, conversely, disrupt circuits implicated in cognitive processing (Kalbe *et al*, 2009; Schroeder *et al*, 2002, 2003; Thobois *et al*, 2007), reducing notably 'cognitive flexibility' (Witt *et al*, 2004). Deficits have been reported in an abnormal metabolic cognitive network (PD-related cognitive pattern) associated with memory and executive dysfunction in nondemented PD patients, which is not influenced (i.e., not improved) by STN DBS (Huang *et al*, 2007a,b) in

contrast to the motor-related pattern (PD-related covariance pattern) (Asanuma *et al*, 2006; Hirano *et al*, 2008).

Effect of DBS on emotional processing and behavior: Deep brain stimulation of STN can induce a wide range of behavioral and mood changes in PD (Appleby *et al*, 2007). Among these behavioral and mood changes, manic episodes have been reported (Mallet *et al*, 2007; Ulla *et al*, 2006). One recent single case study showed that mania induced by STN DBS was associated with an increased activation of the dorsal ACC, which is consistent with what is classically found in bipolar disorders (Figure 3B; Blumberg *et al*, 2000; Ulla *et al*, 2006). This STN-DBS-induced ACC dysfunction could explain the difficulties in performing Go/NoGo reaction time tasks (Hershey *et al*, 2004) and the emotional lability of these patients. However, another study did not confirm this finding and found, in contrast, a decreased ACC activation (Mallet *et al*, 2007). These discrepancies may be partly because of differences in electrode placement but these results need confirmation on a larger group of patients. Interestingly, acute depression induced by DBS of the STN has also been shown to be associated with ACC and prefrontal over-activation; which could mean that the kind of mood changes induced by DBS may vary on the basis of the precise location of the electrode and the presurgical psychiatric state of the patient (Bejjani *et al*, 1999). Another single report using functional MRI has also shown that

depression induced by DBS of the STN was correlated with changes in mesolimbic cortical structures, especially the superior and medial (Brodmann's area (BA) 9/10) prefrontal and anterior cingulate cortices (BA 24), anterior thalamus, caudate, and brainstem (Stefurak *et al*, 2003).

In addition, several studies have shown that bilateral STN stimulation disturbs negative emotional information processing with an impairment of the recognition of fear or anger in facial expressions (Dujardin *et al*, 2004). These difficulties have been related to a deficit of activation of the right fusiform gyrus, which is involved in the processing of emotion in visual stimuli, when PD patients were viewing emotionally expressive faces in the on-stimulation condition (Geday *et al*, 2006; Phan *et al*, 2002). Another recent study using PET and FDG showed that the deficit induced by DBS of the STN in recognition of emotion from facial expressions, especially fear, was related to a dysfunction of the orbitofrontal cortex, a region classically involved in emotion processing (Le Jeune *et al*, 2008).

Another important issue is the induction of apathy after STN DBS in some patients (Drapier *et al*, 2006). The improvement in apathy by dopaminergic drugs suggests that the worsening of apathy in some cases after surgery may be related to a reduction of these treatments after surgery (Czernecki *et al*, 2008). However, the reason why some patients develop apathy whereas others do not remains unknown. Therefore, further functional imaging investigations of the mechanisms of development or worsening of apathy after surgery for DBS of the STN are required.

Altogether, these imaging studies clearly show that the limbic changes associated with DBS of the STN are related to modifications of the functioning of limbic networks. They again reveal a differential action of DBS of the STN on the motor, associative, and limbic BG-frontal circuits.

Effect of DBS on vegetative/autonomic functions: Little data are available with regard to the effect of DBS of the STN on autonomic function, but some studies have shown that this therapy improves autonomic symptoms and fluctuations, such as drenching sweats (Witjas *et al*, 2007). In addition, weight gain has consistently been reported after DBS of the STN (Barichella *et al*, 2003). This weight gain has been related to a restoration of normal resting energy expenditure (Montaurier *et al*, 2007). Another aspect of the nonmotor signs that may be influenced by DBS of the STN is sleep. Several studies have indeed shown that DBS of the STN improves sleep architecture (Arnulf *et al*, 2000). Some data have also shown in PD that DBS of the STN positively influences urodynamic parameters during storage phase (Finazzi-Agro *et al*, 2003). A recent study has found that this improvement in urinary bladder function is related to a decreased activation of the ACC and lateral PFC during bladder filling in on-stimulation condition (Herzog *et al*, 2006). It has been suggested that DBS of the STN improves continence, which in turn leads to a reduction in the activation of areas involved in the maintenance of continence.

Does DBS have a neuroprotective effect?: Some animal experiments have suggested that DBS of the STN could be neuroprotective (Piallat *et al*, 1996). However, functional imaging studies using PET and ^{18}F -Dopa, which allow the analysis of the rate of dopaminergic degeneration, failed to show any neuroprotective effect of DBS of the STN in PD (Hilker *et al*, 2005). Nevertheless, to draw definitive conclusions with regard to this question, it would be of interest in the future to include a control group.

Does STN DBS increase striatal dopamine release?: Some animal studies have suggested that STN DBS could increase the extracellular content of striatal dopamine release (Bruet *et al*, 2001). However this was not confirmed using PET studies and [^{11}C]-raclopride, a D2 dopamine antagonist ligand (Strafella *et al*, 2003b; Thobois *et al*, 2003). Nevertheless, this does not rule out the idea of increased striatal DA release with STN DBS. Indeed, [^{11}C]-raclopride has relatively poor sensitivity for detecting low levels of DA release. In fact, as the test-retest variability of [^{11}C]-raclopride binding in normal subjects under baseline conditions is between 7% and 13%, we can assume that small variations of DA release, leading to a smaller modification of [^{11}C]-raclopride binding, may be within the range of this baseline variability and thus difficult to detect when using such a radioligand (Volkow *et al*, 1993). Therefore, if STN DBS increases striatal DA release, this phenomenon will remain of small magnitude.

Functional imaging studies in dystonia and tremor

Dystonia is characterized by an excess of brain activation leading to sustained muscle contractions inducing abnormal postures and movements. The causes of dystonia can be divided into two broad groups: primary and secondary dystonias. Although the latter refers to dystonia that is primarily a result of specific factors (such as exposure to certain medications, lesions of BG, or trauma), the precise cause of primary dystonias is unknown, although it has become clearer that they are likely to have a genetic basis. In addition, in patients with primary dystonia, brain MRI is normal in contrast to secondary dystonias. In primary dystonia, overactivations were found in the DLPFC, premotor cortex, ACC, cerebellum, and putamen, whereas a decrease in rCBF is usually observed in the primary motor cortex (Ceballos-Baumann *et al*, 1995b; Detante *et al*, 2004; Ibanez *et al*, 1999; Kumar *et al*, 1999; Playford *et al*, 1998). Conversely, in secondary dystonia, rCBF is often increased in the primary motor cortex (Ceballos-Baumann *et al*, 1995a). Other studies on writer's cramp and Meige's syndrome have shown an altered somatotopic representation, which contributes to the loss of functional selectivity of muscle activity (Delmaire *et al*, 2005).

Few studies have analyzed the impact of GPi DBS on the abnormalities of brain activation in dystonia. Two studies have been conducted in generalized

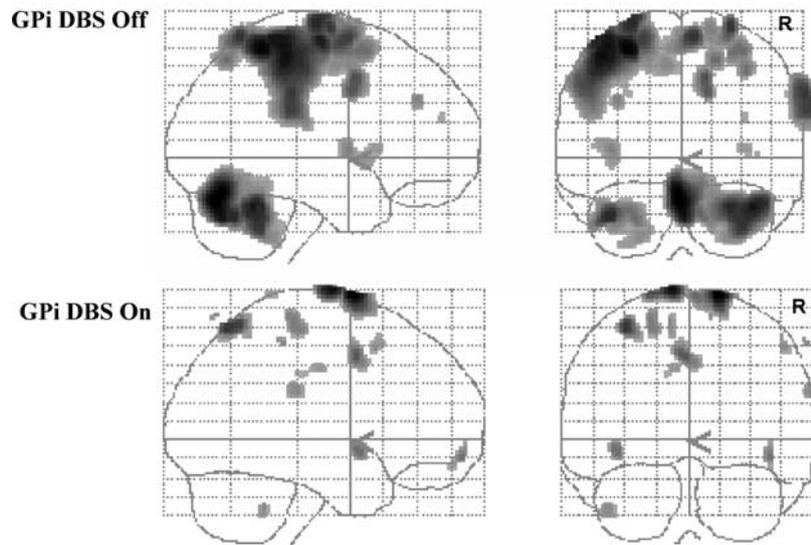


Figure 4 Decreased activation induced by GPi DBS during motor execution in a group of patients with tardive dystonia. PET H₂¹⁵O study. Data are superimposed on coronal and sagittal sections of a glass brain.

primary dystonia, and both showed during motor execution a major reduction in brain overactivity, including, notably, in the prefrontal cortex (Detante *et al*, 2004; Kumar *et al*, 1999). In tardive dystonia, similar results were obtained, but the stimulation-induced decrease mostly involved the cerebellum and primary motor cortex (Figure 4; Thobois *et al*, 2008). These convergent data clearly show that GPi DBS in dystonia acts through the restoration of a selective brain activation pattern and the suppression of the recruitment of inappropriate cortical regions.

Deep brain stimulation in movement disorders was first applied to treat severe tremor (essential or parkinsonian tremor) (Benabid *et al*, 1993). The pathophysiology of essential tremor is still a matter of debate, but the implication of the cerebellum is widely accepted (Lorenz and Deuschl, 2007). In parkinsonian tremor, hyperactivation of the cerebellum has been shown (Deiber *et al*, 1993; Fukuda *et al*, 2004). This hyperactivation is reversed by thalamic DBS (Deiber *et al*, 1993; Fukuda *et al*, 2004). In addition, thalamic DBS induces a reduction in the sensorimotor cortex activation ipsilateral to stimulation (Fukuda *et al*, 2004).

Functional imaging studies in psychiatry

As noted in the Introduction, the field of DBS has expanded and is now under investigation in psychiatric disorders such as depression or OCD (Mallet *et al*, 2008; Mayberg *et al*, 2005). For instance, stimulation of the ventral ACC (BA 25) has been applied to severely depressed patients with promising results (Mayberg *et al*, 2005). This surgical

approach to treat medically refractory depression has been based on convergent data, suggesting that this region is involved in sadness and in the modulation of negative affect (Mayberg *et al*, 1999). In addition, it has been shown that successful antidepressant treatment by medication or other approaches led to a reduction in the activity of this region (Mayberg *et al*, 2000). In accordance with these data, before surgery, a hyperactivation of the ventral ACC (BA 25) and a hypoactivation of the dorsal ACC were observed in depressed patients. Several months after surgery, concomitantly with an improvement in depression, an increased activation of the dorsal ACC and a decreased activation of the ventral ACC were observed (Mayberg *et al*, 2005). The latter result fits well with the conclusion of the meta-analysis of emotion activation studies conducted by Phan *et al* (2002), showing that sadness was significantly associated with activity in ventral ACC. This result is also in line with many theories of the functions of the medial prefrontal cortex suggesting functional divisions within the ACC, the ventral section being more implicated in limbic processing and the dorsal section in cognitive tasks (Amodio and Frith, 2006; Koski and Paus, 2000; Margulies *et al*, 2007).

In OCD, a dysfunction in the orbitofrontal, ACC, striatum, and thalamus has been found (Rauch *et al*, 2006). Stimulation of a ventral striatum/ventral capsule target led to a significant activation of orbitofrontal and anterior cingulate cortices, striatum, Gpi, and thalamus (Rauch *et al*, 2006). Furthermore, metabolic studies showed that stimulation of the anterior capsule induced a decrease in prefrontal metabolic activity, especially in the subgenual ACC, which is considered to reflect an interruption of the cortico-thalamo-striato-cortical circuit (Van Laere *et al*, 2006). In addition, the degree of improvement

in OCD inversely correlated with the metabolism of the left ventral striatum, amygdala, and hippocampus (Van Laere *et al*, 2006). All these findings support a major role for the dysfunction of the limbic circuits in OCD pathophysiology and show that DBS modulates these pathways.

Conclusion

Functional imaging with PET has provided a unique window for analyzing *in vivo* the consequences of DBS on brain activation patterns and has been applied to various disease that benefit from this surgical approach. These studies provide crucial information for a better understanding of the disease itself and, conversely, for clarifying the mechanism of action of DBS. All these imaging studies show that DBS finely tunes specific circuits depending on the task and the underlying disease. As previously suggested, the results of imaging studies also show that the effects of DBS of the STN are task specific and depend on the particular networks engaged by specific tasks (Thobois *et al*, 2007). This fits well with animal studies, which suggest that subcortico-cortical connectivity depends on brain state, such as whether the animal is at rest or active (Magill *et al*, 2004, 2006; Sharott *et al*, 2005). Furthermore, it has been proposed that the mechanism of action of STN stimulation is not merely inhibitory or excitatory but could at the same time inhibit the soma of STN neurons and excite the projections from STN neurons or fibers passing near STN or other nuclei (McIntyre *et al*, 2004). It is possible that the balance between the inhibition of soma and the excitation of axons could be different for specific neural networks engaged by particular tasks. This could explain, for example, the differential effect of STN stimulation on the different frontostriatal circuits during motor versus cognitive tasks.

In addition, the functional imaging approach clearly shows that stimulating a very small structure such as STN induces complex modifications of the pattern of brain activation involving entire networks and not only isolated regions. Therefore, the findings of these studies have to be interpreted in terms of functional connectivity between different brain areas, leading to a better knowledge on how one region interacts with others (Thobois *et al*, 2007). In addition, independently of the therapeutic action of DBS, these surgical procedures when combined with imaging represent a unique *in vivo* opportunity in humans to directly 'manipulate' the functioning of specific structures and to understand the functions of these structures.

One of the critical points in relation to the interpretation of the results of functional imaging studies is the precise location of electrodes, to determine which of the motor, associative, or limbic territories are affected by stimulation depending on the topography of stimulation. In the same manner, a

better understanding of the diffusion of the electrical field around the electrode is crucial and would enhance our understanding and interpretation of the results from imaging studies (Maks *et al*, 2009; Vasques *et al*, 2009). In addition, as most functional imaging studies have investigated modifications of brain perfusion, the study on the consequences of DBS in terms of changes of neurotransmitter release remains largely unknown and would be of great interest. Therefore, in future, this imaging methodology will continue to offer an incomparable window into the mechanism of action of DBS, which, 20 years after the introduction of this surgical approach, is still incompletely understood (Kringelbach *et al*, 2007).

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Disclosure/conflict of interest

The authors declare no conflict of interest.

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