Combining functional imaging with brain stimulation in Parkinson’s disease

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Abstract

Brain stimulation techniques such as deep brain stimulation (DBS) and transcranial magnetic stimulation (TMS) constitute promising clinical and research tools to investigate neural mechanisms underlying neurological and psychiatric diseases. They have enormous potential in modifying brain activity and subsequent function. However, it is still a matter of debate how either of these stimulation approaches operates to produce the clinical outcomes observed in patients. The combination of these techniques with functional neuroimaging is contributing significantly to disentangle the mechanisms through which brain stimulation affects neuronal activity and related networks. In the present review we outline the research done to date on the effects of DBS and TMS on motor, cognition and behaviour in Parkinson’s disease (PD) with particular emphasis on neuroimaging.

Introduction

In neurological conditions that exhibit overactive and underactive brains areas, such as Parkinson’s disease (PD), different forms of stimulation can be used to modify the firing patterns of affected areas. Transcranial magnetic stimulation (TMS) can depolarize neurons within the targeted area and provoke action potentials. This kind of stimulation has also been shown to alter the levels of the neurotransmitters involved in such neuronal deficits (Strafella et al., 2001, 2004). To reach and stimulate subcortical areas that show an abnormal firing activity in PD, a surgical approach uses deep brain stimulation (DBS) to continuously apply electrical pulses that relieve PD motor symptoms (Krack et al., 2002; Moro et al., 2010), with variable effects on cognitive symptoms (Campbell et al., 2008). DBS can be applied in different subcortical targets, each with different efficacy for symptom relief. Similarly, TMS can be applied over the cortex to interfere with the affected area by enhancing or decreasing deficient cortical regions, also known to have downstream effects into other cortical and subcortical regions (Siebner et al., 2009).

The present review will provide an overview of the literature regarding the effects of both DBS and TMS on PD motor, cognitive and behavioural functions. We will focus in particular on those studies that have used neuroimaging methods to attempt to elucidate the mechanisms of these stimulation techniques. It is clear that these approaches combined can reveal the basic functional mechanisms that contribute to both the disease process and the outcomes following treatment with brain stimulation.

Subcortical stimulation in PD

DBS of the subthalamic nucleus (STN) has been recognized as an efficient therapy for patients with PD (Krack et al., 2002). Despite its effectiveness, the precise mechanism of action of DBS remains uncertain (Benazzouz & Hallett, 2000; Hallett, 2000; Kringlebach et al., 2007). Below we will summarize the observations obtained using functional imaging that has provided some insights into the neural substrates underlying the motor and cognitive changes that occur with DBS.

Imaging motor effects of deep brain stimulation

Studies evaluating metabolic and blood flow changes in cortical areas during STN-DBS have consistently revealed a stimulation-related change in the abnormal motor network (Asanuma et al., 2006; Geday et al., 2009; Hershey et al., 2003; Trost et al., 2006). Of particular note, DBS has been found to result in a decreased expression of the abnormal metabolic motor network (Asanuma et al., 2006), previously described by Eidelberg and Edwards (2000), and characterized by an increase in metabolic activity in the pallidal-thalamic and motor cortical area,
produces different results. medial prefrontal cortex however, the two therapies as well as increases in the precuneus. In the STN and DBS and levodopa therapy. They found that both et al. (2006) compared the metabolic effects of STN symptoms of PD via similar mechanisms. Asanuma STN DBS and dopaminergic therapy improve the In this regard, imaging data may elucidate whether some of the improvements seen after STN ers are warranted in humans in order to discover larger studies using more sensitive imaging biomark-

ing of the STN via lesion or DBS may exert neuro-
disturbances and freezing in advanced PD (Stefani et al., 2006; Limousin et al., 1997; Strafella et al., 2003; Thobois et al., 2002).

Regarding the functional changes during STN-DBS in subcortical structures, the literature is more equivocal. In fact, while some studies reported a reduced metabolism in the putamen and the internal part of the globus pallidus (GPI) (Asanuma et al., 2006; Trost et al., 2006) others described an activation of the STN and the directly connected GPI (Geday et al., 2009; Hilker, 2010). Such discrepancies might reflect the complex mechanism of action of DBS, which is more than a simple inhibition or activation of the target.

The study of the effect of DBS-STN on striatal dopamine (DA) transmission using intracerebral microdialysis in animals suggests that stimulation might act directly and/or indirectly on striatal DA levels (Bruet et al., 2001). However, functional imaging using [11C]raclopride, a D2 dopamine receptor antagonist ligand, failed to show any change in striatal dopamine release (Strafella et al., 2003; Thobois et al., 2003), but this may be due to the relatively poor sensitivity of raclopride for detecting low levels of DA release (Ballanger et al., 2009a). That said, numerous preclinical studies have shown that silencing of the STN via lesion or DBS may exert neuro-modulative effects on nigral dopamine neurons (Piallat et al., 1996; Rodriguez et al., 1998). Thus, larger studies using more sensitive imaging biomarkers are warranted in humans in order to discover whether some of the improvements seen after STN DBS can be attributed to changes in DAergic levels. In this regard, imaging data may elucidate whether STN DBS and dopaminergic therapy improve the symptoms of PD via similar mechanisms. Asanuma et al. (2006) compared the metabolic effects of STN DBS and levodopa therapy. They found that both STN DBS and levodopa therapy were associated with significant metabolic reductions in the putamen, sensorimotor cortex and cerebellar vermis, as well as increases in the precurcousus. In the STN and medial prefrontal cortex however, the two therapies produces different results.

Imaging data has so far failed to provide a satisfactory conclusion to the neuroprotective effect of STN-DBS on PD. On one hand, in fact, Hilker et al. (2004), using 18F-Dopa, a marker of presynaptic neurodegeneration, demonstrated a continuous decline of dopaminergic function in patients with advanced PD under clinically effective bilateral STN DBS, with a rate of progression within the range of previously reported data from longitudinal imaging studies in PD. However, controlled studies including different measures of neuroprotection are needed, as striatal 18F-Dopa uptake reflects dopa-decarboxylase activity, which tends to be subject to up-regulation in dopamine-deficient states, thus misestimating the degree of nigrostriatal neuronal loss. Therefore, studies using less regulated presynaptic markers of dopaminergic dysfunction, such as [11C]-dihydroxydiphenyl-2-picrylhydrazine (DTBZ), may be more suited to test the real neuroprotective effects of DBS.

The STN is not the only target for DBS used for PD patients. DBS of the GPI is also effective in improving motor function in PD patients (Follett et al., 2010; Moro et al., 2010). 18F-FDG and positron emission tomography (PET) have revealed that the neural correlates of GPI-DBS in PD, as for the STN-DBS, are consistent with a stimulation-specific reduced expression of the PDRP, which was shown to correlate with clinical improvement (Fukuda et al., 2001b). During a motor task, GPI-DBS has been reported to induce an enhancement of motor activation responses in the SMA and ACC (Fukuda et al., 2001a), with a pattern of activation selective for different aspects of motor performance. Contrary to STN-DBS (Limousin et al., 1997), no significant change was observed in the DLPFC, which may reflect the different connectivity profiles of the STN and GPI to non-primary motor areas.

Recently it has been proposed that DBS of the pedunculopontine nucleus (PPN) may improve gait disturbances and freezing in advanced PD (Stefani et al., 2007). To date, few studies have reported that unilateral PPN-DBS increases regional cerebral blood flow (rCBF) in different subcortical areas, most notably the thalamus bilaterally (Strafella et al., 2008), and the mesencephalic locomotor region, as well as different cortical areas involving medial sensorimotor cortex extending into caudal SMA (Ballanger et al., 2009b).

*Imaging cognitive/behavioural effects of deep brain stimulation*

While the motor improvements following DBS are well accepted, whether DBS impacts non-motor functions is more controversial. It is, however, acknowledged that this issue must be addressed so that safety issues can be fully disclosed to patients,
Brain stimulation and neuroimaging show particular deficits in verbal fluency possible cognitive deterioration in more elderly 1999; Pillon et al., 2000), and less safe in terms of reported as safe by some authors (Ardouin et al., 1999; Pillon et al., 2000). However, such studies are contested by those findings where no changes, or even DBS-induced improvements to cognitive functions were observed (Alegret et al., 2001; Ardouin et al., 1999; Pillon et al., 2000). A major contributor to these inconsistencies is the lack of control samples without DBS (but see Alegret et al., 2001; Gironell et al., 2003; Smeding et al., 2006; Witt et al., 2008).

Neuroimaging studies can extend our understanding of DBS-induced cognitive/behavioural problems by showing alterations in brain function that occur when stimulation is turned on. While these measures may sometimes not be clinically relevant on their own, they are assumed to constitute some of the underlying constructs that determine patients' overall cognitive ability. For example, poor performance on a stop-signal reaction time task (SSRT's) when comparing on versus off DBS may indicate an increase in impulsive behaviour induced by DBS. In the next section we will describe some of the fMRI and PET studies performed while patients were on and off DBS that also measured patient's performance on cognitive tasks. Some of these tasks have a distinct motor element (as in the aforementioned SSRT task), but all involve to some extent cognitive control of the movement to be executed.

The most frequently studied cognitive paradigms are those related to response inhibition (see Logan & Cowan, 1984). Neuroimaging in the healthy brain has revealed that a distributed cortical and subcortical network controls our ability to inhibit unwanted actions. Brain areas identified to be responsible for normally functioning response inhibition include, but are not limited to, the inferior frontal cortex (IFC), pre-supplementary motor area (pre-SMA), the ACC and the STN. The study of response inhibition in patients with PD may be important for understanding the putative emergence of impulsive behaviours in Parkinson's patients treated with DBS. Parkinson's patients are found to perform poorly on measures of response inhibition (Gauggel et al., 2004; Obeso et al., 2011), and this ability is altered by DBS (Ray et al., 2009; van den Wildenberg et al., 2006). How these behavioural effects are manifested, however, is not clear. DBS has been shown to impair, improve and to make no change to patients' ability to inhibit responses (Ballanger et al., 2009c; Campbell et al., 2008; Hershey et al., 2004; Jahan-shahi et al., 2000; Thobois et al., 2007; Witt et al., 2004). These inconsistencies may be explained by the more general improvement on the task due to improved motor control (Ray et al., 2009), disso-ciable temporal effects of stimulation that result in increased impulsive response as well as improvement in the engagement of inhibitory processes (Wylie et al., 2010). Further, it has been shown that differences in the effect of STN DBS on inhibitory control may depend on the exact site of stimulation within the STN (Hershey et al., 2010).

PET imaging has allowed us to visualize the brain as we apply DBS during response inhibition tasks. Campbell et al. (2008) used PET and [15 O]-H2O to measure STN DBS-induced variability in motor response inhibition. Blood flow was found to be altered in the ACC, and this change correlated with the change in response inhibition induced by DBS. This suggested that stimulation of the STN may induce changes in the cortical (i.e. ACC) control of response inhibition. This study also reported that changes in performance induced by DBS on a working memory task was correlated with altered blood flow in the DLPFC. The alteration in working memory may also be important to the study of DBS-induced behavioural changes related to impulsive conditions. Differences in types of response inhibition have been noted (i.e. proactive inhibition, in which the person is aware that the upcoming trial contains a stop signal, and retroactive inhibition, in which information regarding the positioning of stop-trials within a task is not given). Ballanger et al. (2009c) measured blood flow during a Go/NoGo and a control (Go) task to study response inhibition deficits associated with STN-DBS. The PET results revealed that changes on the task were accompanied by reduced activation in areas such as the left premotor cortex, pre-SMA, dorsal ACC and IFC. These areas are thought to sub-serve retroactive response inhibition and to be responsive to salient stimuli that need fast adaptation.

Behavioural complications have been noted after DBS of the STN. Apathy is the decrease or lack of motivation to previously attractive stimuli, and occurs in about 14% of the PD population in the absence of depression (Braak et al., 2004). After STN DBS, apathy has been reported as a highly probable complication (Drapier et al., 2006). Further, it has been proposed that apathy may be the clinical expression of the prefrontal-basal ganglia disruption, involved in the generation and control of self-generated purposeful behaviour (Reijnders et al., 2010). Morphometric data have shown a grey matter reduction associated with apathy, specific to frontal areas (Le Jeune et al., 2009) and to the limbic loops of
fronto-striatal regions (Thobois et al., 2010). Thobois et al., (2010) used [11C] raclopride PET to investigate dopaminergic abnormalities in apathetic PD patients with DBS before and after methylphenidate, a blocker of dopamine transporter. They found greater binding potential in the apathetic patients (compared to non-apathetic PD patients) in mesolimbic areas in the baseline condition and a reduced capacity to release dopamine. PET studies using higher affinity ligands sensitive to extrastriatal D2 receptor availability should confirm their results. Finally, hypomania following STN DBS, particularly when the stimulation was applied via the contact over the anteromedial STN, i.e. limbic loop, confirms the presence of distinct functional modalities that converge in the STN (Mallet et al., 2007).

Cortical stimulation in Parkinson’s disease

TMS is a non-invasive technique that induces electrical currents into the cortex. It has been extensively used in both neuroscience and neuropsychiatry over the last two decades providing relevant observations to the underlying mechanisms of brain activation and de-activation in different neural networks. The reason for its extended use in the research and clinical environments is it can rapidly modulate brain activity and therefore function, by depolarizing neurons or their axons (Siebner et al., 2009).

Imaging TMS effects in PD

One of the main uses of TMS is to study cortical excitability in neurological conditions. With the paired pulse TMS protocol, two stimuli separated in time (conditioning and test stimuli) are delivered to the selected area (e.g. motor cortex (M1)). It is known that short intervals (1–6 ms) between the two stimuli will elicit intracortical inhibition (ICI) and long intervals (8–16 ms) will produce an intracortical facilitation (ICF) (Kujirai et al., 1993). Studies using single and paired TMS pulses between motor areas may reveal inter-hemispheric and intra-cortical inhibition or facilitation (Cantello, 2002) and can provide important information on the pathophysiology of neurological diseases. In PD, dopamine deficits lead to a dysfunction within the cortico-basal ganglia-thalamo-cortical pathways. TMS has contributed significantly to the clarification of PD pathophysiology by detecting, at early stages of the disease, important differences in neuronal activity. Bares et al. (2003) reported that PD patients (naïve to dopaminergic medication) had a reduced bilateral inhibition and facilitation in cortical motor areas compared to controls. A defective ICI and ICF in PD patients has been consistently reported in more severe PD patients (Berardelli et al., 1996; Strafella et al., 2000; Vacherot et al., 2010; Valls-Sole et al., 1994) and it has been shown to be associated with some parkinsonian symptoms such as gait (Vacherot et al., 2010). Vacherot and colleagues (2010) recently demonstrated that PD patients with significant gait impairment (off medication) may have an ICF different from controls. Further, when they recorded motor-evoked potentials from the tibialis anterior muscle, ICF was impaired with a correlation between gait disturbances and ICF.

The magnetic coil can deliver pulses in a repeated fashion where frequency, number of pulses and intensity of stimulation can be controlled with different consequences on the cortex, and therefore on behaviour and cognition (Siebner et al., 2009). For example, repetitive TMS (rTMS) at frequencies greater than 1 Hz tend to increase cortical excitability. However, the effects of rTMS also rely upon the pattern in which the repetitive trains are delivered. A high-frequency pattern of stimulation known as theta burst stimulation (TBS) delivers a train of three pulses at 50 Hz every 200 ms between 20 to 40 s (Huang et al., 2005). TBS delivered at continuously at low intensities (cTBS) produces suppression of motor cortex excitability, but if the bursts are applied intermittently (iTBS) and repeated every 8 s, the effects become facilitatory for up to 40 min. However, its use requires safety considerations since not every patient is suitable (Rossi et al., 2009).

rTMS and TBS are often used for investigating cortical functions. For example, using 1 Hz rTMS over the right DLPFC in healthy participants, a deficit was found in estimation of time perception (Koch et al., 2003). However, with a different rTMS protocol, using 5 Hz rTMS over the right DLPFC, the same group later found an improved time perception ability in PD patients (Koch et al., 2004), an effect absent after rTMS over the SMA. Along the same line, inhibition of familiar responses measured with the Stroop test showed improved performance after 5 Hz rTMS of the left DLPFC (Pal et al., 2010) but not with 10 Hz rTMS, which did not enhance patients’ executive functions (Sedlackova et al., 2009). Recently, 25 Hz rTMS stimulation of the right IFC produced enhanced performance of a Stroop test (Srovnalova et al., 2011). The combination of TMS with imaging techniques has provided relevant information for understanding TMS effects and how clinical benefits may take place based on neurotransmitter release or network activation in remote regions from the stimulated area. For example, one study applied 1 Hz rTMS for 25 min over the premotor cortex and found decreases of metabolic activity in bilateral premotor, SMA and basal ganglia in dystonic patients (Siebner et al., 2003). In healthy participants at rest using high frequency rTMS (10 Hz) over the left DLPFC, dopamine release was...
increased in the ipsilateral caudate (Strafella et al., 2001) as well as the ACC and the medial orbitofrontal cortex (OFC) (Cho & Strafella, 2009).

Some studies have tried to correlate clinical measures (Unified Parkinson Disease Rating Scale part III (UPDRS-III)) and dopamine levels in PD patients after rTMS (Khedr et al., 2007; Kim et al., 2008). Following 2 days of 5 Hz rTMS over the more affected motor area in off-medicated PD patients, a reduced binding in $^{[11C]}$-raclopride was shown in the contralateral caudate nucleus (i.e., greater dopamine release), and significant UPDRS-III benefit was observed (Kim et al., 2008). In addition, after 6 days of 25 Hz rTMS over the right and left M1 in un-medicated PD patients, results showed increased serum dopamine levels that correlated with UPDRS-III improvement after stimulation (Khedr et al., 2007).

The use of rTMS with PET imaging can aid our understanding of the pathophysiology of PD. For example, Strafella et al. (2005) used $^{[12]}$-raclopride and rTMS to compare the symptomatic hemisphere against the asymptomatic hemisphere in early onset patients. The patients received 10 Hz stimulation over both the symptomatic and the asymptomatic M1. They found an ipsilateral release of dopamine in the putamen, but the ‘symptomatic’ putamen had a larger cluster of change in $^{[11C]}$-raclopride binding than the asymptomatic hemisphere, perhaps reflecting a loss of functional segregation of cortical input into the striatum (Strafella et al., 2005). The combination of rTMS with PET may serve to recognize the underlying neurochemical abnormalities in PD and the progressive loss of fronto-striatal connectivity.

As mentioned above, rTMS and TBS are also potential therapeutic tools (due to their long-lasting effects) in a variety of neurological and psychiatric diseases. Indeed, an initial report on depressed patients revealing some improvement after rTMS (Pascual-Leone et al., 1996) opened the door to its application to other diseases such as PD. So far, reports have been inconsistent. A number of studies have reported a therapeutic effect of rTMS in PD. rTMS can transiently influence PD abnormal motor functions (Filipovic et al., 2010; Hamada et al., 2008; Helmich et al., 2006; Khedr et al., 2006; Lefaucheur et al., 2004; Mally & Stone, 1999a, 1999b; Pal et al., 2010; Siebner et al., 2003) with a selective improvement for levodopa-induced dyskinesias (Filipovic et al., 2009; Koch et al., 2005, 2009), especially when high stimulation frequencies are used (Lefaucheur et al., 2004). rTMS at 1 Hz may also elicit a sustained or prolonged change in PD cortex excitability as revealed by a longer silent period duration (Filipovic et al., 2010) suggestive of an influence on GABA activity. However, besides these positive reports, others have failed to show any improvement and have thus rejected claims for a beneficial role of rTMS in PD motor symptoms (Benninger et al., 2011; Boylan et al., 2001; del Olmo et al., 2007; Ghabra et al., 1999; Tergau et al., 1999). A number of reasons may account for these discrepancies, such as methodological differences, patient selection and the role of medication. Animal and human studies have shown that rTMS effects may also depend on the status of synaptic activity in the stimulated region (Todd & Ridding, 2010). Indeed, when 6 Hz stimulation is applied first for a short period, then the inhibitory feature of 1 Hz stimulation is enhanced (Iyer et al., 2003). This strongly suggests that brain activity can be differently excited if patients are drug-naïve or when comparing off versus on medication, or off versus on DBS. Similarly, a cumulative effect should also be considered (Hayashi et al., 2004; Khedr et al., 2006). Some studies reported greater motor improvement as measured by the UPDRS-III after the fourth week of rTMS, but not before (Hamada et al., 2008). Another important point to keep in mind is the placebo effect which can play a key role in rTMS and influence striatal dopamine release (de la Fuente-Fernandez et al., 2001; Strafella et al., 2006). Thus, placebo-controlled studies are a necessary requirement when considering TMS for clinical applications where a symptomatic improvement is expected.

So far there have been also some attempts to stimulate directly the motor cortex with epidural electrodes surgically implanted. A few studies have suggested that this invasive stimulation may be effective in treating the symptoms of some motor disorders (Nguyen et al., 1998) and possibly to be effective for PD as well (Canavero et al., 2002, 2003; Woolsey et al., 1979). However, other studies found no improvement (Moro et al., 2010). Cilia et al. (2008) also observed only limited clinical benefit using this stimulation technique, but using single photon emission tomography (SPECT), found significant rCBF decrements in the pre-central gyrus, pre-motor cortex and caudate nucleus bilaterally, as well as left prefrontal areas and right thalamus.

Conclusions

The concurrent use of DBS or TMS and neuroimaging has provided useful information on the functional role of cortical and subcortical areas in motor, cognition and behaviour, and on the therapeutic role of brain stimulation in PD. DBS can directly modify neuronal populations through still unclear mechanisms. However, clarification of both rCBF and pre-/post-synaptic DA changes must be measured in vivo during DBS to provide direct measures of activation and/or deactivation in the surrounding neuronal structures. This data will reveal how DBS can provide...
symptom relief or aggravation. Further research should also aim to include other neurotransmitters known to interact with DA such as serotonin.

**Take home messages**

Neuroimaging may be a critical component in investigating how neural networks are affected by brain stimulation.

DBS and rTMS are able to alter dysfunctional brain into normal activation patterns.

**Future directions**

Neurotransmitters other than dopamine need to be studied in future research to establish their contribution in the pathogenesis of neurological and psychiatry diseases.

Cortical and sub-cortical stimulation need to be combined together, along with neuroimaging to study neural interactions between different networks and circuits with the aim to obtain better treatment outcomes.

**Declaration of interest:** A.P.S. is supported by the Canadian Institutes of Health Research (MOP-110962), the Edmond J. Safra Philanthropic Foundation and the Canada Research Chair Program. The authors alone are responsible for the content and writing of the paper.

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