Mind over matter: an analysis of the mechanism of deep brain stimulation in the treatment of Parkinson's Disease

EDUCATION

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No conflicts of interest to declare

Accepted for publication: 20.08.2019

ABSTRACT

Relevance:

In a population of increasing longevity, neurological disorders are becoming more prevalent – placing a large strain on NHS resources and funding, as well as an emotional burden on those affected and their families. One such example is Parkinson's Disease (PD). This neurodegenerative disorder of the basal ganglia is characterised by a progressive loss of nigrostriatal dopaminergic transmission, commonly presenting as tremor, bradykinesia, rigidity, postural instability, akinesia, and impairments in cognition. Deep brain stimulation (DBS) has proven a successful approach to treating PD despite its mechanism of action being unclear.

Summary:

Three main problems of counteractive outcomes present when identifying a common mechanism of DBS within targets. Firstly, contrasting actions of DBS are required to explain DBS between targets, such as the GPe and GPi. Secondly, conflicting studies have reported both excitatory and inhibitory action of DBS within the same targets. Finally, the treatment has also paradoxically proven effective in treating hyperkinetic disorders, such as Dystonia. There remains no conclusive model for the treatment's mechanism.

Take Home Messages:

To deliver effective treatment and care, it is important for doctors to understand the mechanism of action of procedures they are performing. Hence further investigation into PD aetiology and DBS action is required.

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In his 1817 Essay on the Shaking Palsy, James Parkinson first described the symptoms of the eponymous disease – distinguishing resting tremor (a pill rolling action) from essential and intention tremors. It was not until the turn of the twentieth century that attempts were made to target Parkinson's Disease (PD) via surgical intervention; however, many were unsuccessful due to hemiplegia often being induced. In 1940, Russell Meyers pioneered basal ganglia lesioning in PD treatment, reporting improvement of both rigidity and tremor. In 1947, Ernest Spiegel and Henry Wycis lead a shift of treatment towards electrical coagulation procedures on the basal ganglia and thalamic nuclei. And in 1952, the implanting of electrode contacts into subcortical nuclei began. (1) This would ultimately become deep brain stimulation (DBS).

However, this work was soon overshadowed by the discovery of dopamine's modulatory effects by Arvid Carlson and colleagues in 1957. Three years later, a deficit in striatal dopamine concentrations was crucially implicated in PD aetiology by Oleh Hornykiewicz, who then went on to pioneer Levodopa (L-DOPA) therapy which remains a first line treatment for the disease. In 1963, an application of DBS to PD was pioneered by Bekthereva and colleagues. (2) Via use of pacemakers, it became the first controlled and reversible PD therapy and met FDA approval in 1997 for the treatment of PD and idiopathic tremor. DBS also proved useful experimentally as it allows for double blind trials. As summarised in Figure 1, three basal ganglia pathways have been implicated in the control of movement. Multiple structures involved in these pathways are approved targets for DBS, including: the subthalamic nucleus (STN), globus pallidus Internus (GPi), and the ventral intermediate nucleus of the thalamus (VIM). The globus pallidus externus (GPe), subthalamic nucleus/Substantia nigra pars reticulata (STN/SNr) combined, and GPe/GPi combined DBS have also proven successful in treating the disease within laboratory conditions.

Despite its mechanism remaining unclear, DBS replaced lesioning therapies as the most common surgical option for PD patients who, though still responsive to pharmacological management, suffer from periods of severe motor complications or dyskinesia. To this day, PD medications can only alleviate symptoms; none stop or delay the degeneration of nigrostriatal neurons. Furthermore, there is at current a 50% chance of patients with early onset PD developing drug-induced dyskinesias within 5 years of pharmacological management. (3) DBS offers a reversible alternative with fewer reported side effects.
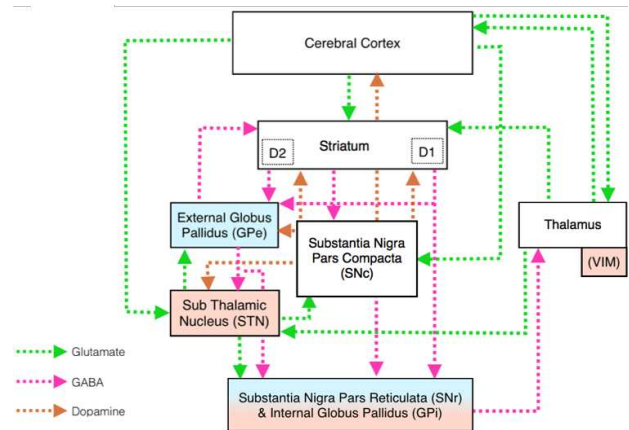
Figure 1: Diagram of basal-ganglia connections. Pink nuclei denote approved DBS targets for PD and blue shaded structures are those which have been successful in experimental studies. Note Direct (cortico-striato-nigral), indirect (cortico-striato-pallido-subthalamo-nigral), and hyperdirect (cortico-subthalamo-nigral) pathways.

Models of Parkinson's Disease

At present there are three leading models for the progression of Parkinson's disease.

The first is changes in SNr/GPi Firing Rates. Here depleted concentrations of dopamine result in both a reduction of tonic inhibition of the indirect pathway and excitation of the direct pathway. Cumulatively, this results in reduced striatal inhibition of the SNr/GPi output nuclei. This model explains bradykinesias and akinesia. Conversely, increased SNr/GPi activity may explain hyperkinetic disorders such as Dystonia. However, tremors are poorly accounted for.

PD tremors have instead been suggested to be result of oscillatory GPe–STN–GPe activity. (4) Here reduced dopaminergic modulation of the indirect pathway results in a continuous cycle of GPe inhibition, STN disinhibition, reciprocal glutamatergic GPe excitation, STN inhibition, and the cycle continues. This model is supported by DBS electrode recordings of PD patients showing oscillatory local field potentials in the basal ganglia. (5)

A third, rather elegant model suggests that temporal differences of activity in direct, indirect, and hyperdirect pathways induce GPi/SNr 'dynamic activity' to alter thalamic input in a centre-surround formation. This is supported by triphasic GPi responses of early excitation, inhibition, and subsequent excitation. (6) Initial thalamic motor commands are reset by hyperdirect pathway action, then the direct pathway disinhibits centre thalamic field to execute

a motor command. Lateral inhibition maintains suppression of surrounding commands. Finally, delayed indirect pathway activity diffusely inhibits all commands. In PD, a deficit of dopaminergic transmission increases the ratio of indirect: direct pathway firing. The consequent temporal shortening and spatial narrowing of GPi inhibition, helps explain the PD symptoms of bradykinesia, akinesia, and rigidity. This broad thalamic disinhibition increases probability of competitive motor commands being generated, resulting in involuntary movements: tremors.

DBS Configuration

The modern-day DBS system consists of three components:

- A lead containing electrode contacts at the tips (often Tungsten) which create a cylindrical contact with the surrounding tissue to stimulate the target.

- An extension wire passing under the skin of the head, neck, and shoulder.

- A pacemaker, often subclavicular, generating a controllable pulse of stimulation to the lead.

DBS leads are commonly one of two variants: monopolar or bipolar. The former involves implanting a cathode contact within the targeted structure. The pacemaker acts as the anode, creating a spherical stimulation field at the cathode. As current flow is greatest at proximity to the cathode, anodal implantation is not performed during monopolar DBS. Bipolar DBS involves both contacts within a single lead being inserted and connected to a pacemaker in the chest cavity. These contacts, less than 1mm apart, create elliptical stimulation fields allowing for a more precise targeting of tissue. Alternative 'multipolar' methods of DBS are under research to assess whether they may offer greater therapeutic benefit. One such example is tripolar DBS with two cathodes and one anode. (7)
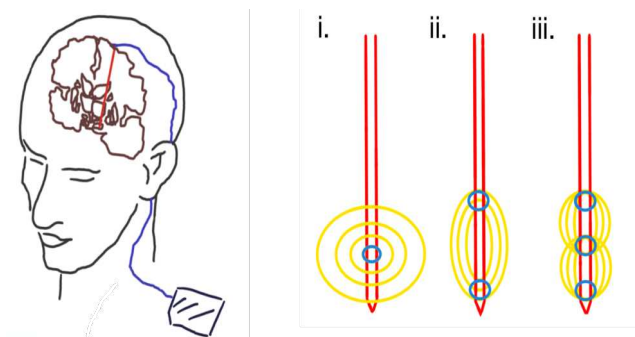
Figure 2 : Left: Diagram of DBS components: the electrode (here targeting the STN) is shown in red and is connected via a lead (blue) to a subclavian pacemaker (grey). Right: Not-to-scale representation of DBS electrode variations and their respective stimulation fields (i. monopolar, ii. bipolar, and iii. tripolar).

Monopolar DBS is the most popular as it requires a lower level of stimulation to attain identical therapeutic benefit to bipolar DBS as the space between contacts is greater, therefore a larger volume of tissue is activated. Hence, battery longevity is greater and fewer operations to replace batteries are required.

The pacemaker system itself can also be one of two types: voltage-controlled stimulation (VCS) and current-controlled stimulation (CCS). (8) Adapted from cardiac pacemakers, VCS is the traditional approach. However, as the immune system targets the foreign electrode, tissue builds up at the contacts. This results in impedance changes and consequently current fluctuations and charge accumulation, ultimately leading to over-stimulatory side-effects. To counter this, and maintain a constant output, a parallel arrangement of capacitors absorbs surplus charge and discharges when needed. This increases pacemaker size and mass, making implantation more invasive. The uniform flow of electrons in CCS overcomes these issues. However, this requires a large output headroom and a lower voltage swing compared to the near 100% attained by VCS. The amount of charge supplied, and its rate of delivery can be controlled by adjusting the pulse width, current/voltage supply, and the frequency of stimulation. As current fluctuations are absent in CCS, it is easier to control pulse width than in VCS.

'Excitation vs. Inhibition' Debate

As there is no unanimously accepted PD model, it is unsurprising that contradictory effects of DBS action have been reported in PD treatment. This paper will now explore DBS action within individual targets.

i. GPi-DBS

GPi stimulation was shown in 1996 to alleviate rigidity and bradykinesia in MPTP treated monkeys. (9) As pallidotomies were a successful approach in the 1990s, GPi-DBS was long accepted to act via inhibiting neurons. However, a reduction of activity in 77% of sampled, responsive thalamic neurons (mostly VA and VLo) in an awake macaque monkey indicates that the GPi is instead excited by DBS. (10) Only 16% of the thalamic neuron pool were shown to have a higher rate of firing during GPi stimulation. The decrease in thalamic activity was suggested to obstruct abnormal firing patterns causative of PD. Additionally, increased thalamic activation has been explained by antidromic current propagation during GPi-DBS treatment of Dystonia patients. (11) The excitation model is further

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supported by recordings of decreased primary motor cortex activity during GPi-DBS. (12)

GPi stimulation is often performed at 130-185Hz, 60–90µs pulse width, and at a constant voltage of 1–3.6V – parameters optimal for exciting GPi axons rather neural soma. (6) Hence GPi-DBS action may be due to downstream excitation via GPi efferent neuronal current spread, despite a reduction or no change in the activity of the GPi itself. However, this is further complicated by GPi-DBS studies on PD monkeys reporting multiphasic responses of both excitation and inhibition. This may be due to activation of both GABAergic and glutamatergic terminals. (13)

ii. STN-DBS

As lesioning of the STN significantly reverses PD symptoms in MPTP treated monkeys (14), initial studies hypothesised STN-DBS to act via inhibiting STN activity. (15) This was thought to be via a depolarisation blockade; however, voltage gated channel inactivation has also been recently proposed. (16) Later studies reported that 44% of STN neurons inhibited by high frequency stimulation exhibited both early inhibitory and rebound excitatory phases; thus indicating a role of hyperpolarisation. (17) Furthermore, VL neuronal activity increases during STN-DBS, indicating inhibited STN-GPi input (18)

Conflicting studies report increased GPi and GPe activity of MPTP treated monkeys during STN-DBS. (19) Additionally, a trial on 10 PD patients showed SNr activity to be increased during and 10 minutes after 130Hz STN stimulation. (20) Hence it is likely that if STN neurons are excited during local DBS, they consequently stimulate GPe, GPi, and SNr neurons via efferent glutamatergic projections.

An explanation for this confliction is that STN-DBS inhibits the soma of STN neurons while simultaneously exciting their axons, resulting in downstream stimulation of interconnected basal ganglia nuclei. (21) This explains unchanged activity in GP neurons despite reduced STN activity and firing rates in other nuclei being similar to stimulation pulse rate. Additionally, this mechanism has been proposed to incorporate antidromic activation of GPi-STN efferents, though their presence is inconsistent with other anatomical studies. (22).

A study has also suggested STN-DBS to both inhibit and excite different populations of STN neurons. (23) These effects were attributed to stimulation of glutamatergic and GABAergic afferent axon terminals. Stimulation also increased SNc activity, possibly explained via STN-SNc efferent activation.

iii. GPe-DBS

GPe stimulation alleviates bradykinesia and akinesia in Parkinsonian monkeys. (24) This induces a repeating cycle of GPi suppression, brief activation, and 5ms latent prolonged suppression, restoring SNr/GPi firing rates to those seen in non-Parkinsonian monkeys. Additionally, oscillatory GPe and STN activity is reduced, hence supporting all three PD models.

GPe-DBS has also been shown to excite and inhibit different GPe neuronal groups. (6) GPe neurons receiving single-pulse stimulation exhibited either a biphasic neuronal response of initial inhibition and subsequent excitation or prolonged inhibition with no excitation. Repetitive stimulation produced both excitatory and inhibitory effects.

Biphasic activity of neurons may be due to post-hyperpolarisation rebound spiking. Differing effects between neuronal groups can be explained in line with the excitation model of DBS: variances in densities of neurons projecting into the GPe induce differing responses to GPe stimulation. (25) This is supported by injections of GABAA antagonist Gabazine eradicating inhibitory response to stimulation and combined administration of AMPA and NMDA channel blockers NBQX/CPP abolishing excitatory effects. The Oscillatory Firing Pattern model of PD also explains the biphasic recordings: an inhibition of the GPe during DBS would decrease activity of GPe-STN GABAergic neurons, in turn disinhibiting the STN and increasing activity of STN-GPe glutamatergic neurons. This would result in phases of inactivation and activation of the GPe in an oscillatory manner.

iv. Combined DBS

A trial has recently investigated the therapeutic benefit of GPe-DBS, GPe/GPi combined-DBS, and pharmacological PD management in patients who had previously undergone GPi-DBS. (26) GPe-DBS was more effective than GPi-DBS. However, combined DBS was by far the most effective treatment, suggesting a synergistic mechanism. GPi-DBS was more effective treatment in the long run. As observed earlier, excitation of GPe and inhibition of GPi best explain the effects of DBS in line with the firing rate and oscillatory firing pattern models. GPe/GPi combined-DBS evidently presents a paradox. I suggest that these contradictory effects may be explained by activation of glutamatergic afferents in the GPe and GABAergic terminals in the GPi. However, this specificity of DBS targeting is contradicted by many of the aforementioned observations of mono GPe- and mono GPi- DBS. Combined GPe/GPi-DBS doesn't fall in line well with the dynamic activity PD model.

Additionally, a double-blind study suggested STN/SNr combined-DBS as a novel treatment in alleviating PD refractory gait disturbances. (27) This is supported by SNr (mono)-DBS alleviating forelimb akinesia in hemi-Parkinsonian rats. (28)

v. VIM–DBS

The ventral intermediate nucleus (VIM) of the Thalamus receives input mainly from the cerebellum and projects to the primary motor cortex to aid in the coordination of movement. Bypassing the basal ganglia entirely, unilateral VIM-DBS was as beneficial as, and produced similar side-effects to, unilateral thalamotomy. However, stimulation is reversible and also safer to use on elderly patients. It was hypothesised that the mechanism of this is via inhibiting neurons of a transcortical reflex loop. (29) A 6-year multicentre follow up study showed monopolar VIM-DBS to significantly reduce contralateral tremor with p-values of < 0.00001. (30) Additionally, a > 60% decrease in average contralateral tremor scores in the 'off-state' was observed compared to baseline figures, suggesting that VIM-DBS induces permanent physiological changes in alleviating tremor. The nucleus remains a DBS target in alleviating upper extremity tremor and is easier to surgically access than the STN.

Disruption Hypothesis

Following their work identifying GPi-DBS to inhibit both artificial cortical response and spontaneous discharge via activation of GABAergic afferents, Chiken and Nambu hypothesised a third DBS mechanism: GPi-DBS activates afferent axon terminals and dissociates them from efferent projections, hence 'blocking' the flow of information through the output nucleus. (6) The mechanism for this is in essence synaptic fatigue; stimulated neurons excessively release neurotransmitter and so cannot respond to further action potentials as their transmitter stores have been depleted.

A disruption model of DBS action would fall in line with all three PD models as any abnormal PD basal ganglia activity – be it firings patterns, rates, or dynamic activity changes – passes through the GPi. The mechanism may also explain the counterintuitive efficacy DBS has in treating dystonia: involuntary movement commands, as explained by the dynamic activity model, are blocked by GPi stimulation. Based on reports of direct pathway inhibition of the SNr not being affected by STN stimulation (31), it was also suggested that STN-DBS 'blocks' hyperdirect and indirect pathway excitation of the SNr. This would explain the treatment's ability to alleviate bradykinesia and rigidity in PD patients.

Discussion

Depolarisation blockade, voltage-gated channel inactivation, and GABAergic afferent activation have been suggested to explain inhibitory effects of DBS action. Axonal stimulation, particularly of glutamatergic afferents, has also been proposed to account for DBS's excitatory effects.

Evidently there is a contradiction in action of DBS. Based on the

disruption hypothesis, this review suggests that these observations are in fact not antagonistic but rather synergistic in nature. Observed effects vary due to glutamatergic and GABAergic neuron pools being investigated, but in either case excessive transmitter release reduces abnormal information flow in the stimulated nucleus.

I also suggest that this hypothesis may explain the sustained effects of DBS when stimulation is turned off. That is, prolonged stimulation of afferent axon terminals may instigate a long-term depression mechanism due to excessive bouton polarisation. A reduction of neurotransmitter release sites on the presynaptic membrane would decrease response to action potentials, essentially 'blocking' information flowing through. Support for this comes from hippocampal GABAergic synapses exhibiting a long-term reduction of GABA release probability as result of presynaptic NMDA-mediated calcium influx. (32)

GPe-DBS is likely explained by an increase in GPe activity or the activation of GABAergic efferents projecting to the STN. However, GPe-DBS may also be explained by a disruption mechanism. As the GPe has been shown to have high intrinsic activity (33), stimulation disrupting GPe input would result in greater inhibition of the STN and output nuclei. This falls in line with Vitek and colleagues' study explored earlier. (24) Additionally, tremor symptoms may be alleviated due to reduced GPe-STN oscillatory firing.

However, the disruption hypothesis raises some issues. Firstly, in the STN and GPi the suggested effects are near indistinguishable with those supporting the inhibition hypothesis. Secondly, reduced direct pathway activity, as a result of nigrostriatal neurodegeneration, is not compensated for by GPi-DBS in this hypothesis. If anything, the remaining direct pathway input to the GPi is too being blocked by this mechanism, along with hyperdirect and indirect pathways, resulting in intrinsic GPi firing. As PD symptoms are drastically reduced to near-normal values of symptom scores, this hypothesis undermines previously held views of the role of the basal ganglia in motor control. Thirdly, a study on rodent optogenetics showed selective activation of hyperdirect (cortico-STN) neurons to alleviate PD symptoms. (34) This contradicts an STN-DBS mechanism of disrupting hyperdirect pathway information flow. Furthermore, observations of post-inhibitory rebounds after stimulation cannot be accounted for by disruption as the tissue is polarised. Instead a delay and subsequent neurotransmitter release would be expected.

Conclusion

The STN and GPi are approved targets effective in alleviating debilitating PD symptoms. For those suffering from tremor dominant PD, additional benefit may be found from VIM-DBS. Though parameters vary by the structure targeted, effective

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DBS ranges are 130-200Hz frequency, 60-100μs pulse width, and 1-5.5V constant voltage. Monopolar DBS requires a lower level of stimulation and hence offers more optimal battery life. However, bipolar and multipolar approaches are favourable for those with side effects from stimulation. GPe, SNr, and combined DBS may offer alternative future strategies.

DBS has been shown to induce both inhibitory and excitatory effects. A disruption view of DBS action may explain a synergy between these observations. However, this may also be explained by Moran et al.'s hypothesis of simultaneous somatic inhibition and axonal stimulation. Although, a disruption mechanism would account for the benefit of DBS in treating hyperkinetic disorders.

Generally, the firing rate PD model seems to best explain the inhibitory effects of DBS. While both inhibitory and excitatory hypotheses of DBS action fall in line with oscillatory firing patterns. The disruption hypothesis supports both of these models as well as Nambu et al.'s work on 'dynamic activity'.

As there is no unanimously agreed representation of basal ganglia connections, there remains no absolute model for PD aetiology, and consequently a lack of consensus on DBS action. There is no question that DBS has proven an effective approach to PD therapy and has paved the way for examining basal ganglia action. However, further investigation into the relationship between cortico-baso-thalamic connections and PD is required to gain a better view on the mechanism of DBS and refine its application in PD treatment.

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