Neuroscience: Therapy modulates decision-making in Parkinson’s disease

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There is mounting evidence that decision-making can be affected by treatment in Parkinson’s disease. A new study shows that dopamine and deep brain stimulation, two mainstay treatments of Parkinson’s, differently affect how patients make decisions weighing rewards against effort costs.

People with Parkinson’s disease express a range of symptoms affecting movement, cognitive, motivational and emotional domains. While therapy can markedly improve movements and also alleviate impairments in other functional domains, there is increasing evidence that it can have detrimental effects on decision-making abilities1–6. A new study by Pagnier, Asaad and Frank7, reported in a recent issue of Current Biology, confirms this and demonstrates that different treatments — dopaminergic medication and deep brain stimulation of the subthalamic nucleus — have distinct, separable effects on decision-making tested within a single task and patient group.

Parkinson’s disease is characterized by the progressive degeneration of neurons that are crucial for the controlled release of neurotransmitters, in particular dopamine8. This affects various functions required for physiological, adaptive behaviour. For example, patients express altered sensitivity to rewards and effort costs associated with actions (Figure 1A) resulting in impairments of motivation and movement6. Albeit rare in early stages, many patients develop cognitive problems in the course of the disease, some of which can be improved, while others are worsened by dopaminergic medications10. Thus, it can be difficult to disentangle whether behavioural changes in Parkinson’s disease are related to disease pathology or instead to therapy1,12.

The introduction of the dopamine precursor levodopa in the 1970s revolutionized treatment of Parkinson’s disease, which had previously mainly been treated with non-dopaminergic medication or neurosurgical lesioning of basal ganglia areas13. Due to long-term complications of levodopa treatment, in particular involuntary dyskinesia movements, and the newly emerging possibility for continuous electrical stimulation instead of lesioning of the basal ganglia, there was a renaissance of neurosurgical treatment of Parkinson’s disease in the early 1990s13. In deep brain stimulation surgery an electrode is implanted in the basal ganglia, in Parkinson’s disease most commonly the subthalamic nucleus, and an electrical current continuously applied at high frequencies (~130 Hz) and an amplitude of several mA. This can lead to a marked clinical improvement and allows reducing dopaminergic medication, thus alleviating dopaminergic side effects. Unintended effects related to dopaminergic medication are not limited to dyskinesia. It has become increasingly clear that a significant proportion of patients develops abnormal, impulsive behaviour — so-called impulse control disorders comprising compulsive shopping, eating and sexual behaviour as well as pathological gambling, in particular when treated with dopamine agonists5,14.

While subthalamic deep brain stimulation allows reducing dopaminergic medication and related side effects such as impulse control disorders, it can itself have unintended effects. In particular, it has consistently been observed that patients with subthalamic deep brain stimulation do not take sufficient time for deliberation before committing to a choice1–3,25, which can be conceptualized as a reduction in the decision threshold (see below and Figure 1B). This observation leads to a clinical conundrum: if patients treated with subthalamic deep brain stimulation tend to
make decisions more impulsively, why is the occurrence of impulse control disorders reduced after surgery? The study by Pagnier, Asaad and Frank sheds important light on this seeming contradiction.

Pagnier et al. recruited nine patients with Parkinson’s disease who were treated with dopaminergic medication and subthalamic deep brain stimulation. While the original design was more complex including stimulation with low and high frequencies (low frequency stimulation was omitted from the main analysis) and stimulation of contacts located higher or lower in the subthalamic nucleus (both conditions were combined), the data were analysed in a 2-by-2 design with the factors dopamine (normal medication versus 12 h withdrawal) and deep brain stimulation (turned on versus turned off).

Thus, within the same patients, effects of dopamine could be contrasted with effects of deep brain stimulation. Patients performed a task in which they had to decide between options with low effort (gripping force) and low reward (money) versus options with high effort and high reward. In a clever design, the options were first titrated to find the indifference point (the combination of effort and reward where patients were equally likely to choose either option) and then options on either side of the indifference point were presented to the patients. To limit fatigue, the actual effort only had to be expended in a random subset of trials.

First, the authors analysed patients’ choices regarding their sensitivity to reward and effort using logistic regression. They found that dopamine increased patients’ sensitivity to rewards and reduced their sensitivity to effort costs (Figure 1C, left and right panels), while deep brain stimulation reduced patients’ sensitivity to both (Figure 1D, right panel).

To investigate these findings in more detail the authors used computational analyses with drift diffusion models. In these models, the relative value of an option is accumulated over time until a certain level of evidence is reached (termed decision threshold) and patients commit to a choice (Figure 1B). In the model that best explained the data dopamine increased the impact of reward and reduced the impact of effort on evidence accumulation. In contrast, subthalamic stimulation reduced the decision threshold (Figure 1D, left panel) leading to faster and more variable decisions near the indifference point. Importantly, these changes were not related to differences in motor abilities, since effort was calibrated to maximal force in each condition. Furthermore, patients with Parkinson’s disease mainly show movement slowness, not weakness.

It had previously been shown that dopamine can increase sensitivity to reward in reward–effort trade-off tasks and that deep brain stimulation reduces decision thresholds. The strength of this study lies in the demonstration of these effects within a single task and patient group and their relation to specific latent mechanisms in a common computational framework. Furthermore, as outlined by the authors, the results might also explain how dopaminergic medication and subthalamic deep brain stimulation differently affect impulsivity in Parkinson’s disease. According to the current study and previous reports, subthalamic deep brain stimulation reduces the time that patients take for deliberation, but leaves other aspects of decision-making unaffected. While this renders patients’ decisions more susceptible to noise (since less time is spent on deliberation), it does not automatically make the content of the decision more risk-prone, nor do patients become unaffected by negative outcomes, two mechanisms that have been related to dopamine-related pathological gambling and other forms of impulse control disorders. Thus, both dopaminergic medication and subthalamic deep brain stimulation can affect impulsivity in Parkinson’s disease, but this relates to distinct mechanisms and different aspects of impulsive behaviour.

There are some limitations to this study including the relatively low sample size and the lack of image reconstruction of the stimulation electrodes. Furthermore, the included patients did not have impulse control disorders. Increasing reward sensitivity might be a beneficial effect alleviating apathetic symptoms in Parkinson’s disease, but decisions that only consider expected rewards neglecting possible costs could also contribute to abnormal behaviour. Including Parkinson patients with impulse control disorders in larger sample sizes might shed further light on this unresolved question.

Figure 1. Distinct effects of dopamine and subthalamic stimulation on decision-making in Parkinson’s disease. (A) In effort-based decision-making expected rewards are weighted against effort costs associated with the choice. Patients with Parkinson’s disease express increased sensitivity to effort costs and reduced sensitivity to reward. (B) In drift diffusion modelling relative evidence (in this task given by the reward and effort costs) for one option over another is accumulated over time until a certain amount of evidence is reached (termed decision threshold) and an option is chosen. Reducing this decision threshold leads to faster and less optimal choices. (C) In the current study, dopamine increased patients’ sensitivity to reward and reduced patients’ sensitivity to effort (illustrated in the left panel). In the logistic regression this was reflected by a steeper slope between % accepted high-reward, high-effort options and increases in reward (schematically illustrated in the right panel) as well as a flatter slope between % accepted high-reward, high-effort options and increases in effort (not shown). (D) Subthalamic deep brain stimulation reduced patients’ decision thresholds (left panel), making patients less sensitive to both reward and effort (right panel) and speeding up reaction times around the indifference point (not shown).
Taking these limitations into consideration, this study gives important new insights into mechanisms underlying decision-making and how these are affected by treatment in Parkinson’s disease. It also elegantly demonstrates how studies in Parkinson’s disease can be used as a translational tool to improve our understanding of behavioral control in the human brain20. To gain further insights it will be important to ground future studies in clear behavioural frameworks making specific and empirically testable predictions.

DECLARATION OF INTERESTS
The author declares no competing interests.

REFERENCES

Algal evolution: A touch of brown in a Paleozoic sea of greens and reds
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Previous molecular clock studies indicated a Mesozoic origin for the brown algae (Phaeophyceae). New research based on phylogenetic evidence challenges this notion and provides novel insights into the origin and diversification of brown algae, which includes multiple transitions within the group from isogamy to oogamy (and back again!).

The present-day oceans host a fascinating abundance and diversity of macroalgae, commonly known as seaweeds — marine plants of relatively uncomplicated structure large enough to be seen with the naked eye. The largest of them, Macrocystis, forms towering underwater forests up to 60