Models of Parkinson’s disease revisited

Conventional models propose that activity levels in two neuronal pathways, which have opposing effects on movement, become imbalanced in Parkinson’s disease. Analyses in mice point to a more complex reality. See Article p.177

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Scientists have long associated structures in the forebrain called the basal ganglia with the control of movement, and with movement disorders such as Parkinson’s disease. Some of the strongest evidence for the role of the basal ganglia in movement is anatomical: the basal ganglia receive neuronal input from movement-related areas in the brain’s frontal cortex through a region called the striatum. They then send it back to the frontal cortex. Two pathways mediate this processing, but models to explain how processing functions go awry in movement disorders are debated. On page 177, Parker et al. add valuable data to the discussion.

In conventional models of basal-ganglia function, the two pathways that connect the striatum to output structures work in opposing ways. The first, dubbed the direct pathway, is activated by the neurotransmitter molecule dopamine, through D1-like dopamine receptors on direct-pathway spiny projection neurons (dSPNs). Activation of dSPNs is thought to facilitate movement\(^1\).\(^2\). The second, the indirect pathway, is inhibited by dopamine through D2-like receptors on indirect-pathway spiny projection neurons (iSPNs). In contrast to the first pathway, activation of iSPNs is thought to reduce movement\(^3\).\(^4\).

Current models of basal-ganglia function emphasize that balanced activity in these two pathways is required for normal movement. For example, one model posits that sequential activation of the pathways could ‘scale’ movements — activation of dSPNs would first facilitate movements, and subsequent activation of iSPNs would terminate them.\(^5\). Alternatively, the action-selection hypothesis proposes that interplay between dSPN and iSPN activation might assist the selection of particular actions by the frontal cortex, with initiation of certain movements associated with dSPN activation, and movement prevention associated with iSPN activation\(^6\).\(^7\).

These models predict that movement disorders result from imbalanced pathway activities. For instance, it has conventionally been argued that, in Parkinson’s disease (which involves decreased striatal dopamine levels), the balance would shift in favour of iSPN activation, leading to slowness or lack of movements. By contrast, involuntary movement (dyskinesia), such as that associated with overuse of the anti-parkinsonian drug L-3,4-dihydroxyphenylalanine (L-DOPA), would arise from a shift towards dSPN activation (Fig. 1a).

Parker et al. used a method called fluorescence microscopy\(^8\)\(^9\)\(^10\) to simultaneously monitor the activity and spatial arrangement of large groups of dSPNs and iSPNs in freely behaving mice. The two sets of neurons were genetically engineered to fluoresce when calcium entered the cell, indicating electrical signalling. The authors monitored three groups of mice: those under normal conditions, mice treated with a drug that causes the loss of dopamine-releasing neurons to mimic the parkinsonian state, and dopamine-depleted animals treated with L-DOPA to induce involuntary movements.

The authors’ observations in normal animals

The authors to directly detect viruses in urine and saliva. Their approach can be used to discriminate between related viral species, which can be difficult to tell apart because they cause similar symptoms.

Viral genomes can mutate rapidly, but Myhrvold and colleagues showed that they could use their system to discriminate between sequences that differed by a single nucleotide mutation. This enabled them to identify strains of Zika virus isolated from different geographic regions, as well as a Zika virus harbouring a mutation associated with a developmental condition called microcephaly. They showed that appropriate guide sequences can be designed in less than a week, and the whole protocol implemented in less than two hours, with minimal equipment and sample processing.

The diagnostic tests described in the current papers are a major advance for the tracking and treatment of viral outbreaks. But they could also have diverse applications beyond viral detection, such as identifying tumour-specific cancer mutations for personalized medicine, and enhancing quality control in agriculture and biomanufacturing by detecting possible biological contaminants. Although their long-term shelf-life remains to be tested, the tools excel in all other ASSURED criteria set by the World Health Organization for point-of-care devices\(^8\), and are ready for deployment. The impact and adoption of these technologies will be determined by factors such as regulatory approval, scaling up synthesis for mass production, distribution logistics and economics.

Much of the excitement about CRISPR technology has centred on its use in gene or cell therapies, which are expensive processes that, for the foreseeable future, will probably be available only in prosperous regions of the world. The current studies greatly expand and diversify the possible beneficiaries of CRISPR technology, by developing a low-cost technique that has many important potential uses.\(^*\)

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supported findings in animal models that similarly sized clusters of iSPNs and dSPNs are simultaneously activated during movement. These data contradict both the scaling model (under which dSPNs are expected to be active before iSPNs) and the action-selection model (which predicts that clusters of inhibitory iSPNs should be larger than those of facilitating dSPNs). Instead, they add to mounting evidence that these pathways might not regulate the basic execution of movements. The conventional model does not predict specific spatial arrangements of activated neurons. By contrast, Parker and colleagues find that normal movement in mice involves activation of clusters (indicated in dashed lines) of dSPNs and iSPNs. In the parkinsonian state, dSPN activation is reduced and iSPN activation is increased. Clusters of activated dSPNs are smaller than in the normal state, and active iSPNs are less clustered. The opposite occurs in dyskinesias.

confirmed that similarly sized clusters of iSPNs and dSPNs are simultaneously activated during movement. These data contradict both the scaling model (under which dSPNs are expected to be active before iSPNs) and the action-selection model (which predicts that clusters of inhibitory iSPNs should be larger than those of facilitating dSPNs). Instead, they add to mounting evidence that these pathways might not regulate the basic execution of movement, but might have a role in higher-order behavioural activities, such as the dynamic shaping of movements through reinforcement learning or the control of movement ‘vigour’.

When the authors studied dopamine-depleted parkinsonian animals, they found decreased dSPN activity and increased iSPN activity, as predicted by the conventional models. However, they also found declines over time in the movement-related activation of iSPNs (a phenomenon separate from their general increased activation level), and declines in the spatial clustering of their activation (Fig. 1b).

As expected, drugs that activate D1-like receptors increased dSPN activity in parkinsonian mice, whereas drugs that stimulated D2-like receptors reduced the elevated iSPN firing rates. 1-DOPA treatment, which leads to activation of both receptors, elicited both effects and was the only treatment to reverse the clustering deficit in iSPNs, perhaps explaining its superior clinical efficacy. Finally, these beneficial effects became exaggerated in animals that developed involuntary movements induced by 1-DOPA: iSPNs became underactive, and dSPNs became hyperactive and less clustered.

Parker and colleagues’ study therefore supports many of the general conclusions of earlier work regarding activity changes in the normal, parkinsonian and dyskinetic states. However, it also shows that the conventional models are oversimplified, because they cannot account for the newly discovered changes in spatial clustering of active striatal neurons in disease states.

This study is an excellent example of how far experimental analyses of circuits in the basal ganglia have come in the past few years. Where we could once record a single, unidentified striatal neuron, we can now monitor hundreds of genetically characterized neurons simultaneously, albeit still at a low temporal resolution and at the expense of tissue damage caused by the implanted microendoscope. As Parker and colleagues demonstrate, these techniques can provide insights into disease mechanisms that were not possible with earlier methods. Beyond being of substantial academic interest, the insights afforded by the current study suggest that it might be worth developing therapeutic strategies for the treatment of Parkinson’s disease aimed at decorrelating hyperclustered striatal activity patterns. Similar approaches have been explored using pharmacogenetic techniques and deep brain stimulation in other portions of the basal ganglia.

As with any good study, this research leads to more questions than it answers, particularly with regard to the changes in spatial clustering of active neurons seen by the authors. For instance, the mechanisms governing the opposing abnormalities in clustering in the parkinsonian and dyskinetic states are not understood, and it remains unclear whether they reflect changes in inputs to the striatum, or bona fide striatal phenomena. It is also not known whether similar clustering occurs in humans or other primates, or whether it is accompanied by altered clustering of neuron activity in other basal-ganglia structures.

Only time will tell whether the gradual shifts in cluster sizes found in the parkinsonian and drug-treated animals are related to known adaptive processes, such as the loss of input-receiving structures called dendritic spines on the surfaces of iSPNs and dSPNs, as Parker et al. suggest.

Finally, one of the most important questions is whether the observed changes in the spatial and temporal clustering of neuronal activities in the basal ganglia are, in fact, causally related to aspects of Parkinson’s disease or the development of dyskinesias. Regardless of the answer, Parker and colleagues’ study has added a new dimension to our understanding of the abnormalities seen in this disease.

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