doi:10.1093/brain/awaa463 BRAIN 2021: 144; 357–371 | 357

BRAIN
A JOURNAL OF NEUROLOGY

SCIENTIFIC COMMENTARIES

A space-time continuum in DBS: structural and functional advances in Parkinson's disease

This scientific commentary refers to 'Modulation of beta bursts in subthalamic sensorimotor circuits predicts improvement in bradykinesia', by Kehnemouyi *et al.* (doi:10.1093/brain/awaa394).

Parkinson's disease is a severe neurological disorder causing disabling motor and non-motor symptoms. The relationship between Parkinson's disease and dopamine denervation has long been established; however, how a focal degeneration of neurons in the substantia nigra leads to such widespread network dysfunction has been somewhat of a puzzle. Broadly, two separate lines of research have been investigating this issue with complementary approaches—one structural and the other functional. Early pivotal work by Mahlon DeLong's group showed that subthalamic nucleus (STN) inactivation in a primate model of Parkinson's disease restored motor function, thereby identifying a small and yet critical structural node in the network pathogenesis that drives Parkinson's disease (Bergman *et al.*, 1990). This discovery led to rich structural mapping of nodes within the cortico-basal ganglia loop in order to establish the precise role of different components of this network and identify targets for intervention.

In parallel, significant work has been conducted by a number of groups, notably that of Peter Brown, looking at changes in functional neural signal activity within these nodes during peri-operative mapping. These studies have shown that there is a characteristic subcortical neural population signal in Parkinson's disease called the beta signal (Hammond *et al.*, 2007). This is a brain oscillation with 13–30 cycles per second (Hz) which occurs in bursts and correlates with disease severity, and which is suppressed by levodopa and deep brain stimulation (DBS) (Kühn *et al.*, 2008; Torrecillos *et al.*, 2018).

Both of these research domains have led to advances in DBS therapy, with improved spatial targeting localization to the dorsolateral STN, including directional current steering and recent temporally locked adaptive DBS triggered according to the beta signal. However, the relative importance of structural versus functional targeting in DBS and the precise mechanistic impact of DBS on brain targets and signals have yet to be fully identified.

In this issue of *Brain*, Kehnemouyi and colleagues combine structural and functional approaches together in an investigation of the mechanisms of DBS (Kehnemouyi *et al.*, 2021). The authors use a number of experimental and analytical approaches to achieve the precision needed to interrogate this complex, high-dimensional question. First, to avoid peri-operative microlesion effects that would otherwise impact neurophysiological studies, they used an investigational embedded DBS device that can sense as well as stimulate (Medtronic Activa PC&S). This facilitates recordings in chronically implanted, freely moving, DBS patients and is a strong validation of sensing-enabled DBS devices for propelling discovery in translational neuroscience. The authors made remarkable use of a first-generation implantable recording system to analyse a very small signal in the context of a much larger stimulation artefact (Swann *et al.*, 2018). This technical challenge is now being addressed by second generation implantable sensing devices with improved signal:noise (Gilron *et al.*, 2020). In the present study, Kehnemouyi and colleagues carried out dynamic neural signal analyses (bursts) in addition to classical averages of neural signal power over time (power spectral density). They then used an objective, quantitative movement task that has greater sensitivity than conventional clinical rating scales. Finally, they used a within and across subjects design, which was statistically optimized via linear mixed effects modelling, and combined this with biophysical volume of tissue activation modelling (Horn and Kühn, 2015).

Using these tools, they first replicated a previous finding that conventional, high frequency DBS improves the speed of movement, and then directly related this improvement to changes in physiology and structure. Specifically, they found that beta power and beta burst duration were reduced with increasing stimulation, and that these reductions were associated with changes in hand movement velocities. Decreasing beta power and beta burst duration both predicted faster hand movements. Importantly,

however, the degree of this physiological beta suppression and the impact of DBS on movement speed were critically dependent on the (modelled) volume of tissue activation of the dorsolateral STN. A number of these findings have been shown previously in separate studies. However, this study relates DBS stimulation to structure (dorsolateral STN) and function (bursts of beta oscillations) within individual subjects and links it to changes in motor behaviour in a precise and objective manner. In other words, by modelling both the volume of tissue activation in the dorsolateral STN and the impact of stimulation on neurophysiological biomarkers (beta power and beta burst duration), it is possible to predict motor improvements resultant from DBS, within and across subjects.

This approach has wide neuroscientific and translational applications. First, it supports and unifies previous hypotheses regarding structural and functional determinants of motor dysfunction in Parkinson's disease. Specifically, the findings provide further evidence in support of the 'oscillatory' theory of the disease, showing that dysfunction of beta oscillations and burst dynamics, particularly in the dorsolateral STN, are central to the movement deficits. Furthermore, this study suggests that combining structural and functional approaches can predict outcomes of DBS within individual subjects. This could support principled and rational programming of conventional high frequency DBS and theoretically validates both directional and sensing approaches to supporting DBS targeting and parameter selection (Fig. 1). Advances in DBS technology are delivering ever increasing options for adjustment using directional stimulation and sensing-enabled devices, with the promise of more precise and personalized treatment for patients. However, manual optimization of this expanding high-dimensional parameter space will soon become an intractable problem for clinicians. There is an urgent need for principled techniques to rationalize this process and shrink the search space of DBS parameters to a viable selection of candidate settings.

This study validates a modelling approach to such a solution, combining three input variables: amplitude of beta oscillations, beta burst characteristics and theoretical dorsolateral STN volume of tissue activation to predict stimulation outcomes. Looking ahead, one can see how this approach could be extended to include further candidate power bands (e.g. low frequency theta and high frequency gamma) and alternative recording sites (such as sensorimotor cortex). These additional signals could be combined to better predict stimulation outcomes. As the number of input parameters increases, machine learning and advanced statistical approaches for both classification and stimulation optimization will likely be needed to extract signal from noise and to determine relative spatial and temporal contributions.

A number of challenges remain for future studies, both theoretical and technical. First, it is difficult to

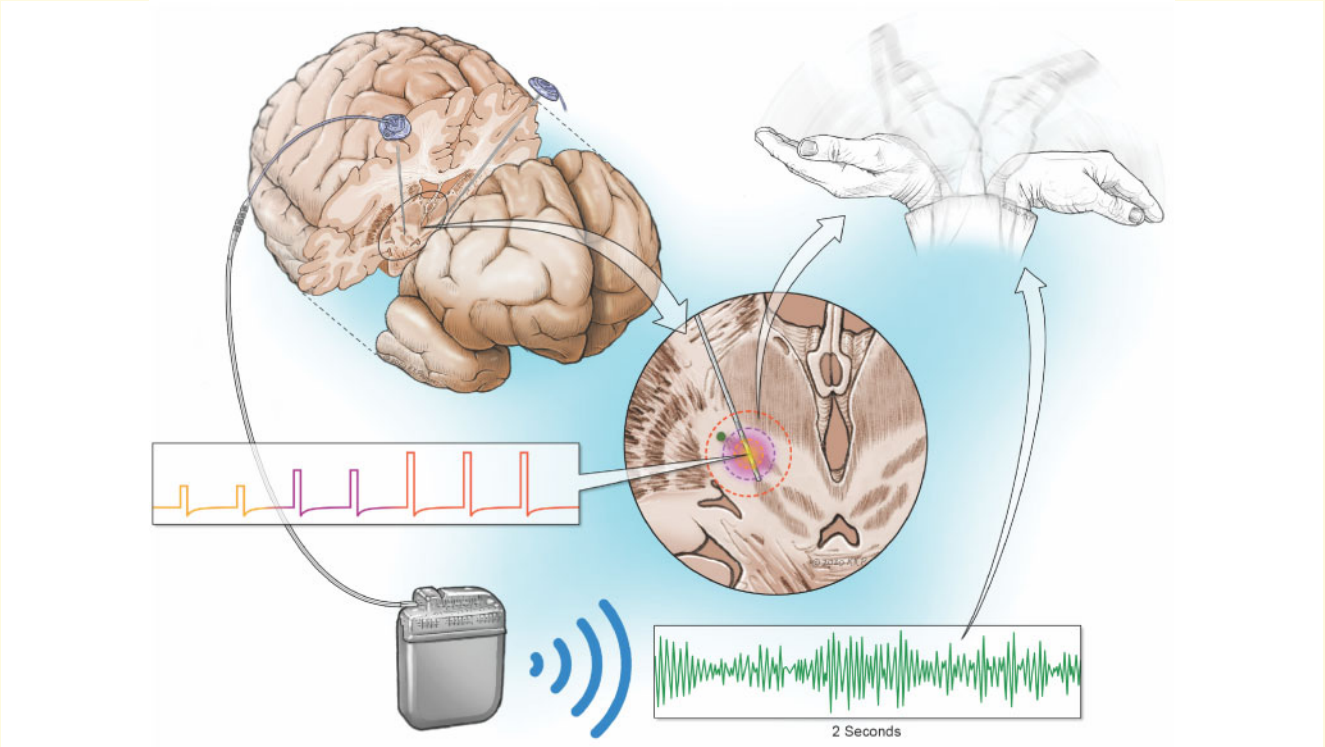

Figure 1 Combining structural and functional approaches to investigate the mechanisms by which DBS improves motor function in Parkinson's disease.

determine whether beta band oscillatory phenomena are truly causal for specific motor signs of Parkinson's disease and this relationship affects how we target specific physiological signals in adaptive DBS. This is not critical when using a pure biomarker approach, as some approaches to adaptive DBS will work perfectly well using state biomarkers (e.g. slow adaptive DBS triggered off average dorsolateral STN beta power). However, other approaches are predicated on these signals being pathological and attempting to directly reshape them (e.g. fast beta burst adaptive DBS). The other challenge is technical—analysing and combining large and complex datasets that include structural and electrophysiological data recorded across a range of different devices is complex and time consuming. The 'Lead DBS' package (https://www.lead-dbs.org/), as leveraged in this study, has demonstrated how successful an open source community-led approach can be to accelerating understanding in the structural domain in movement disorders. A number of efforts are now underway to support open source community-led development of tools and software for neurophysiology analysis, and specifically for sensing enabled neuromodulation devices (e.g. https://openmind-consortium.github.io/), with the aim of accelerating development and analysis on the functional signals side. A long-term aspiration might be to have structural and functional integration combining fine-grained spatial mapping and dynamic electrophysiological recordings in the presence and absence of stimulation.

This study represents a significant step forwards in unifying divergent structural and functional approaches to optimizing therapy in Parkinson's disease. With the recent emergence of sensing-enabled and directional DBS devices, this reconciliation of approaches is especially warranted. It provides a road map for future studies to account for both neural structure and neural signals in movement disorders as they work towards designing better spatially and temporally targeted therapies.

Competing interests

The authors report no competing interests.

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doi:10.1093/brain/awaa463

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Untangling the tau microtubule-binding region

This scientific commentary refers to 'CSF tau microtubule binding region identifies tau tangle and clinical stages of Alzheimer's disease', by Horie *et al.* (doi:10.1093/brain/awaa373).

Human tau exists as six isoforms, all produced mainly by neurons. A range of post-translational modifications, as well as fragmentation by a variety of proteases, together determine the aggregation and propagation potential of tau (Quinn *et al.*, 2018). In general, tau functions are regulated by the phosphorylation and dephosphorylation of combinations of its 45 serine, 35 threonine and five tyrosine residues.

In neurodegenerative conditions involving tau (tauopathies), tau typically accumulates within neurons (and to a much lesser extent in astrocytes and oligodendrocytes), and is released into the brain interstitial fluid as part of physiological processes and upon cell death. Brain interstitial fluid is filtered through the tight junctions of ventricular endothelial cells to become CSF, taking soluble forms of tau with it. CSF circulates through the