

EDITORIAL**Targeting network dysfunction in neurodegenerative diseases**

Reductionist approaches to neurological diseases have proven to be both highly seductive and immensely frustrating. They are seductive because they present simple, elegant mechanistic explanations that, by their very nature, provide targets for drug development. Yet they have also become deeply frustrating. Why? Because it is increasingly apparent that no matter how much we understand about the molecular basis of some diseases, this is insufficient to account either for all their manifestations or to develop effective therapies. Nowhere has this become more evident than in the field of neurodegenerative disorders, which pharma is now loathe to touch. Its fingers burnt by a series of Alzheimer trials with negative outcomes, aspirations of transformative cures are rapidly being replaced by—perhaps more realistic—goals of symptom control.

An alternative to understanding brain diseases at the molecular level is the systems or circuit approach. This rests on relating the clinical manifestations of a disease to the brain networks that are dysfunctional. It has the potential power to explain why a single disease might present in many different ways (because different networks are disrupted by the same underlying molecular pathology), and also why different diseases might present with the same behavioural syndrome (because the same network is dysfunctional across different pathologies). But how might the network approach lead to effective treatments? Moreover, how do we bridge the huge gap between molecular and systems level descriptions?

Animal models might seem the first place to start but although they have clearly become influential, there remain doubts about how well they might actually reproduce the spectrum of phenotypic diversity observed within even a single human disease. For example, while motor symptoms have classically been considered the hallmark of Parkinson's disease it is now appreciated that there is a panoply of non-motor manifestations, including many different cognitive, behavioural and neuropsychiatric syndromes, that can affect patients. How might understanding

the brain networks underlying this diverse range of clinical presentations ever lead to effective, specific therapies?

One possible way is if treatments could be delivered locally to critical nodes within a dysfunctional network. This might seem like a pipe dream. Nevertheless, some recent papers published in *Brain* show how this might be possible to understand the network effects of local deep brain stimulation (DBS) for the motor system. For example, the precise location of DBS electrode stimulation near the thalamic ventral intermediate nucleus has a significant influence on tremor improvement, either of the hand or the head, in essential tremor (Al-Fatly *et al.*, 2019). Structural imaging analysis revealed that the proximity of electrodes to the cerebello-thalamic-cortical pathways in this region was predictive of better outcomes. Functional connectivity, based on resting state functional MRI, again showed that tremor improvement was associated with specific connectivity changes to cortical and cerebellar motor regions.

Similarly, in Parkinson's disease, the precise location of DBS electrodes in the subthalamic nucleus (STN) has a significant influence on resting state functional connectivity throughout the motor network, specifically cortical and cerebellar components (Horn *et al.*, 2019). Indeed, in this pioneering study, which scanned patients on and off stimulation, DBS shifted functional connectivity towards the normal pattern observed in healthy controls. These innovative reports show how it is possible to target motor symptoms, but can such principles be extended to non-motor symptoms? Encouraging signs that this might be possible come from two further papers, also published in *Brain*.

In the first study, the location of STN DBS electrodes in Parkinson's disease was related to changes in non-motor symptoms following surgical implantation (Petry-Schmelzer *et al.*, 2019). The results showed that improvement in mood or apathy scores occurred with stimulation at distinctly different locations to beneficial effects of DBS on cognitive symptoms such as attention and memory. Furthermore, improvements in sleep or fatigue were more

likely to be reported with stimulation just ventral to the STN proper.

In the second study, published in the current issue, the authors used a hypothesis-driven structural imaging approach combined with clinical and experimental behavioural measures to investigate correlates of impulsivity in Parkinson's patients prior to DBS (Mosley *et al.*, 2019). The results showed that different components of impulsive behaviour are associated with differences in the strength of white matter connections involved in brain networks previously identified to play a key role in reward or incentive processing and response inhibition. Relating such structural differences to subsequent impact of DBS on impulse control and functional connectivity of frontostriatal circuits remains to be performed.

These approaches pave the way for a better understanding of the effects of network disruption on clinical presentations. In the long term, they might also extend application of DBS to treatment of non-motor symptoms in Parkinson's disease (Gratwicke *et al.*, 2018). However, in their current form, they still fail to bridge the gap between molecular and network levels of description. This is likely to require innovative means of local drug delivery or novel means by which optogenetic stimulation might be performed in human brains. One recent study in mice demonstrated that specially manufactured nanoparticles (dubbed 'upconverting nanoparticles') can transform near infrared light shone from outside the skull to the blue-green wavelengths required for local optogenetic stimulation (Chen *et al.*, 2018). Using this technique, it was possible to stimulate genetically tagged neurons in the ventral

tegmental area (VTA), causing phasic release of dopamine from the ventral striatum, a major projection of target of VTA neurons. The challenge of genetic vector delivery to tag target neurons in humans remains formidable, but these novel approaches give a glimpse of how it might be possible one day to bring the reductionist and systems approaches a little closer together.

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