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Optogenetics, functional imaging, and computational modeling to develop a diagnostic tool for Parkinson's disease

David Bernal Casas
University College of London, UK

The diagnosis of Parkinson's disease (PD) is based on the observation of clinical symptoms and neurological examinations and significantly relies on the identification of classical motor symptoms. However, the severity of the symptoms varies from person to person, and misdiagnoses and confusion with other illnesses are frequent. To date, no laboratory biomarkers exist for this neurological condition, and findings on functional imaging are not remarkable. Thus, there is a critical need to develop diagnostic tools to assist medical doctors. Our long-term goal is to develop a reliable diagnostic tool for hospitals, a method that may assist physicians to determine the illness. In response to this need, we have designed and developed an interdisciplinary approach to achieve this ambitious goal. Our approach combines two experimental tools with a computational method and uses both animals and humans. The first experimental tool is optogenetics. Optogenetics modifies specific types of neurons so they can be switched on in response to light. Optogenetics now allows for precise spatial and temporal control of the experimental input enabling a broad array of applications to study the responses of neuronal systems. The second experimental tool is functional magnetic resonance imaging (fMRI), which measures blood flow in the brain. We associate increased blood flow with increased neuronal activity. Using optogenetics to switch on a specific type of neuron, and fMRI to map how other regions of the brain respond, we can use computational modeling to generate quantitative descriptions of specific brain networks with cell-type specificity, and also determine its function. Then, we can estimate the contribution of each specific brain network to the same networks estimated in the healthy and diseased human brain and develop a diagnostic tool. Testing our approach to rodents, we have targeted two different types of neurons known to be involved in PD. We found that upon stimulation of a specific type of neurons that has D1-dopamine receptors, we activated a pathway – the direct pathway - that called for greater motion while when stimulating the other type of neurons that has D2-dopamine receptors, we activated another pathway – the indirect pathway – that called for less motion. We then imaged animals while stimulating either type of neuron and showed how the different neuron types generate distinct whole-brain activation maps, maps with different behavioral outcomes. Finally, we designed a computational approach to draw circuit diagrams that underlie these neuron-specific brain circuit functions. For the first time, we published quantitative neural circuits with cell-type specificity. These findings may already help to improve treatments for PD. For instance, medical doctors are already using a technique called deep brain stimulation (DBS) to ameliorate Parkinson's tremors in their patients. In short, DBS delivers tiny electric jolts at high frequency to neurons that are thought to be responsible for the tremors. A better understanding of the how those neurons work to control movement could help guide more effective stimulation therapies. However, more broadly speaking, our approach – optogenetics and fMRI combined with computational modeling – may give scientists a novel way to reverse-engineer the functions of the many different types of neurons in the brain and the humongous diverse array of neural circuits formed to carry out various commands which are responsible for behavior

bernalgps@gmail.com