Abstract

Introduction: The human brain connectome — a map of how different brain regions are connected anatomically and functionally — has shaped our understanding of brain function in health and disease. Our understanding of human network-level brain function has drawn from a range of methods including invasive neurophysiology (depth electrodes and electrocorticography, deep brain stimulation), noninvasive physiology (EEG, MEG, TMS, fMRI/rsfMRI, and noninvasive neuroimaging (PET, MRI)). We review how these methods of studying the human brain connectome have shaped our understanding of movement disorders and are poised to guide development of novel therapeutic paradigms.

Methods: We systematically review the literature to highlight major insights in human brain connectivity learned over the decades from the 1970’s to present day, with a focus on how these insights have shaped our understanding of human movement disorders and neurotechnological therapeutics including DBS and TMS.

Results: In 1972 D.F. Scott described EEG changes in Huntington’s Disease, and in the late 1980’s Neufeld et al. used EEG to describe cortical physiology in Parkinson’s disease. Since that time there has been an explosion of technological advances including multi-site invasive recording in patients undergoing deep brain stimulation, as well as advances in non-invasive structural and functional imaging including diffusion tensor imaging and resting state functional connectivity, which have opened windows into whole-brain pathophysiology of movement disorders including Parkinson’s disease, Huntington’s disease, essential tremor, and dystonia. Furthermore, these findings have begun to suggest targets for therapeutic non-invasive stimulation and for multi-site sensing-stimulation (‘closed-loop’) approaches to invasive stimulation.

Conclusion: Our understanding of the human brain connectome in health and disease is rapidly evolving. In the future, advances in invasive and noninvasive physiology may allow these measures of network dysfunction to be translated into therapeutics targeted at specific network dysfunction.

Purpose

Synthesizing and summarizing historical as well as present day findings will help inform neurologists on new therapeutic applications for movement disorders. Additionally, as we highlight the current gaps in the scientific knowledge we hope to inspire scientists to fill these gaps and pursue further movement disorder treatment.

Methods

A systematic literature review of major milestones in neurological evaluation, there use in discovery of movement disorder pathology and a review of recent outcomes in movement disorder therapies.

History and Advances in Movement Disorders

Huntington’s Disease

- Functional MRI (fMRI) and diffusion tensor imaging (DTI) are used to measure functional and structural brain connectivity, respectively. Functional connectivity is described as the areas of the brain that can be seen in fMRI or positron emission tomography (PET) co-activating together at rest. Resting-state fMRI (rsfMRI) has been used to study how the brain functions as a network and not in isolation.
- Recently, it has been thought that by measuring the electrophysiological connections between these networks using transcranial magnetic stimulation, we may be able to gain a better understanding of connectivity and of neuropathology.

Pallidal target DBS for PD.

- While mapping the functional connectivity of PD, the basal ganglia network has shown to be reliably altered on fMRI in drug naïve L-DOPA patients and may be a reliable diagnostic tool in early preclinical stages of PD.
- New targets for PD, such as the pedunculopontine nucleus, have been found from studies of functional connectivity.

Conclusion/Future Application

- Tuleasca et. al, has shown functional connectivity from the ventro-lateral ventral nucleus of the thalamus to the primary somatosensory and supplementary motor, visual association, or pedunculopontine nucleus after thalamotomy.
- Additionally, Tuleasca et. al. results indicate the strength of interconnectivity in drug-naive essential tremor can predict responses to stereotactic radiosurgical thalamotomy.

Dystonia

- Bolondi et. al, found idiopathic dystonia was associated with abnormal structural connectivity of the middle frontal gyrus, bilateral pallidum and putamen, left caudate, and subcortical postcentral gyrus.
- GPI and pallidal DBS are effective targets for reduction of dystonia symptoms.
- Recently, there has been a study utilizing MEG to understand cortico-pallidal and cerebellar oscillatory connectivity in idiopathic dystonia patients and may have shed light on more optimal targets for continuous DBS

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