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Connecting Mind, Brain, and Seizures by Default Mode

Effective Connectivity Within the Default Mode Network in Left Temporal Lobe Epilepsy: Findings From the Epilepsy Connectome Project

Cook CJ, Hwang G, Mathis J, et al. *Brain Connect*. 2018. doi:10.1089/brain.2018.0600. [Epub ahead of print]; PMID: 30398367

The Epilepsy Connectome Project examines the differences in connectomes between patients with temporal lobe epilepsy (TLE) and healthy controls. Using these data, the effective connectivity of the default mode network (DMN) in patients with left TLE compared to healthy controls was investigated using spectral dynamic causal modeling of resting state functional magnetic resonance imaging data. Group comparisons were made using 2 parametric empirical Bayes (PEB) models. The first level of each PEB model consisted of each participant's spectral dynamic causal modeling. Two different second-level models were constructed: the first comparing effective connectivity of the groups directly and the second using the Rey Auditory Verbal Learning Test (RAVLT) delayed free recall index as a covariate at the second level in order to assess effective connectivity controlling for the poor memory performance of patients with left TLE. After an automated search over the nested parameter space and thresholding parameters at 95% posterior probability, both models revealed numerous connections in the DMN that lead to inhibition of the left hippocampal formation. Left hippocampal formation inhibition may be an inherent result of the left temporal epileptogenic focus as memory differences were controlled for in one model and the same connections remained. An excitatory connection from the posterior cingulate cortex to the medial prefrontal cortex was found to be concomitant with left hippocampal formation inhibition in patients with TLE when including RAVLT delayed free recall at the second level.

Commentary

One exciting aspect of studying epilepsy is the chance to blend wisdom from many different fields of knowledge. For epilepsy, not only does clinical medicine overlap with basic physics and chemistry, but overlaps with humanities such as art and philosophy also emerge. The fact that the disease often involves changes in awareness and perception calls into question the definition of consciousness. Although day-to-day life and clinical practice may not require delving into such heady subjects, the opportunity to do so is omnipresent. Humans have for millennia asked the same question: "What is consciousness?"

For any scholar, the opportunities to ponder such issues may be irresistible. Such is the opportunity offered to us by Cook and colleagues. Although indirectly, the report offers insight into the building blocks of consciousness awareness and how they may be altered in temporal lobe epilepsy (TLE). The study team is impressive, including experts in neurology, psychology, biophysics, and radiology. The report also compels learning new vocabulary—at least new to entrenched clinicians. First, the concept of connectome warrants explanation. Very briefly, a connectome represents the network of white matter connections in the brain. Connections vary among humans based upon genetics, education, cognitive capacity, and experience, though the variability is superimposed upon basic tendencies or modality templates, for example, visual pathways, or language localization in the left temporal lobe, and so on.

The other main concept requiring explanation is the default mode network (DMN). The intrigue of the DMN continues to grow along with its expanding prominence in the medical literature. Most consider the default mode to reflect a passive mental state, such as in daydreaming, resting, or otherwise not directing thoughts in any focused manner. The network itself seems to encompass limbic structures such as the posterior cingulate cortex, medial prefrontal cortex, bilateral hippocampi, and fiber tract connections. Ultimately, the DMN has been described as the neurologic basis for the self.[1]

The idea that the mind actually has a locale in the brain allows for interesting neuropsychological questions to ponder. An anatomical base for mental reflection, including remembering the past, or planning for the future, may vividly represent a blending of the brain and the mind. Philosophers and neuroscientists through millennia have wondered what it is like to be

human, essentially, what it is like to have self-awareness. Descartes, who famously stated, "cogito ergo sum" (I think therefore I am) was perhaps referring to the DMN.[2]

It is intuitive to consider that the DMN is awry in many neurologic diseases, but clarifying those relationships is challenging. Possibly, the state of calm self-reflection lives in the temporal lobe, tapping into capacities of verbal memory. This is the argument of Cook and colleagues, that the default mode may in part reflect a stream of verbal thoughts. If this is true even to some degree, then the temporal lobe's role in language processing and memory would surely be involved. If verbal memory is impaired by underlying temporal lobe seizure foci, then perhaps the DMN is also impaired. Although the recent report by Cook et al has several aims, the impact upon the DMN is perhaps the loftiest among them.

As for most functions in the brain, connectivity is the main driver as opposed to strict roles of functional neuroanatomical regions. The epilepsy connectome project endeavors to incorporate the role of connectivity in seizure propagation, as well as in cognitive function overall. For this study, pathways connecting the posterior cingulate cortex and hippocampal formations were studied in depth, both of which appear to be constituent parts of the DMN. Although the modeling and correction factors may be too detailed for this brief commentary, the upshot is that connectivity differed in those with TLE as compared to controls.

The implications are profound on one level, though the conclusions are difficult to generalize. Although it may be expected that TLE involves rewiring and reconnecting given the pathology of epileptogenic tissue, the idea that the DMN also rewires is uncertain. Do patients with TLE have different default modes? Do they experience the world differently, perhaps with less facility for efficient verbal memory? Is this analogous to other neurologic disorders such as dementia or schizophrenia or even other personality styles, where the default mode may vary in terms of functionality, and by extension, actual network connectivity. The explosion of recent literature suggests that such queries have validity.[3-5]

Epilepsy as an illness has long been viewed as analogous to lesion studies of previous generations in terms of presenting useful opportunities to learn about underlying brain function. Prior to modern imaging studies, lesion analysis was the most efficient way of ascertaining relationships between brain anatomy and function. Today we have new techniques, but the opportunity for epilepsy to teach important lessons about brain function remains. Given our new understandings about the DMN and implications for neural connectivity, the fact that epilepsy leads to changes in this most basic of human brain and mind functionality is meaningful.

Perhaps the self-awareness and experience of the mind for any individual are always altered by neurologic diseases, and thus, the default mode is heterogeneous. Although this may be intuitive, the fact that limbic structures are intimately involved and also at the core of the pathologic findings in TLE allows yet another neurological pathophysiologic explanation for the overrepresentation of psychiatric illness with epilepsy.

By Jay Salpekar

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