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EDITORIAL

# Brain disconnections refine the relationship between brain structure and function

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Efforts to understand the relationship between brain structure and function within the framework of brain networks are not new, far from it. This work began more than a century ago. Carl Wernicke interpreted receptive aphasia in the context of a distributed language network with specialized processing nodes almost 150 years ago (Wernicke 1874). The functional effects of focal pathology on anatomically remote but connected brain areas were conceptualized more than 100 years ago (Von Monakow and Harris 1914; Carrera and Tononi 2014). And a modern understanding of how a brain lesion impacts a distributed network to produce behavioral effects was written more than 30 years ago (Geschwind 1965a, b; Damasio and Damasio 1989). So why is there a surge of interest in the network effects of brain lesions now? Why is a century-old topic in neuroscience suddenly thrust into the spotlight as a hot new topic today?

There are many possible explanations. Perhaps the field of cognitive neuroscience is re-assessing our methodological approaches after an over-exuberant emphasis on functional MRI over the last 30 years. At its peak, it was debated whether fMRI may obviate the need for lesion studies (Rorden and Karnath 2004). But challenges with replication and the underwhelming clinical translation of fMRI findings have hinted that just the opposite is true (Kullmann 2020; Marek et al. 2022). There are distinct advantages to supplementing correlational findings with lesion studies and other methods that allow more robust causal inferences (Siddiqi et al. 2022; Forkel et al. 2022). In this context, the recent surge in lesion studies is addressing a call to rectify the over-reliance on fMRI in recent decades. Another possible explanation relates to the rapid progress of therapeutic brain stimulation for otherwise refractory neurological and psychiatric disorders. One could argue that the potential benefits of accurately elucidating the functional neuroanatomy of the human brain have never been higher; each discovery has the potential to inform a novel therapeutic target or improve upon an existing one. While these explanations likely contributed, the most critical factor contributing to the current renaissance of lesion studies and the investigation of the network effects of focal brain lesions relates, in our view, to new resources available to neuroscientists today to map brain connectivity.

The term "connectome" refers to a comprehensive mapping of the structural and functional connectivity of the human brain (for a historical review see Catani et al. 2013). The Human Connectome Project (http://www.humanconnectome.org/), The Human Brain Project (http://www.humanbrainproject.eu/), and other major international initiatives aspire toward this goal. Worldwide, researchers now have access to rich datasets with high-quality imaging data that can be analyzed to construct maps of the brain's macroscopic wiring diagram, including white matter tracts derived from diffusion MRI and functional connectivity networks derived from correlated patterns of BOLD activity among brain regions. These large datasets have propelled greater collaboration of neuroscientists with data scientists and mathematicians to elucidate the network organization of the

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brain. The results of these efforts are beginning to transform human neuroscience.

Progress in connectome research has paved the way for the disconnectome. This relatively recently coined term refers to the pathological disruption of the connectome and the manifestations of that disruption observed in brain structure, function, and behavior (Thiebaut de Schotten et al. 2015, 2020). The tremendous growth in this line of research over the last decade has motivated this special issue. Investigators have shown considerable ingenuity in combining different methods and imaging modalities to accelerate the rate of discovery in disconnectome research. This special issue serves to coalesce several exciting research lines by leading investigators. We have arranged the articles of this special issue into four groupings that are not mutually exclusive.

First are articles that directly measure disconnection in the human brain in individuals with brain lesions. These analyses highlight the diversity of disconnectome research in including lesions of different etiologies (tumors, stroke, neurodegeneration) and measurements of disconnection using different modalities, including diffusion MRI, functional connectivity MRI, and EEG (Russo et al. 2022; Saviola et al. 2022; Gallina et al. 2022; Sedghizadeh et al. 2022; Godefroy et al. 2022; Toba et al. 2022; Zhu et al. 2022; Bassignana et al. 2022; Egorova-Brumley et al. 2022; De Luca et al. 2022). Second, are articles that indirectly measure disconnections in the brain by inferring disruptions based on imaging from large groups of healthy individuals with high-quality imaging or brain atlases (Thiebaut de Schotten et al. 2015; Boes et al. 2015). Articles in this category include: (Souter et al. 2022; Conrad et al. 2022; Sperber et al. 2022; Hajhajate et al. 2022; Tomaiuolo et al. 2022; Dulyan et al. 2022; Yeager et al. 2022). As with any new field, there are many opportunities to refine and improve the methods of disconnectome mapping. The relative strengths and weaknesses of direct versus indirect measurement of disconnectivity are unclear and require additional investigation. Further, when using indirect methods, there are many open questions, like the relative value of structural versus functional connectivity (Reber et al. 2021; Salvalaggio et al. 2020; Thiebaut de Schotten et al. 2014), how these different modalities can be combined (Bowren et al. 2022), and how much the specific normative datasets used influences the results. The third grouping of articles directly addresses these important methodological questions (Silvestri et al. 2022; Cotovio et al. 2022; Souter et al. 2022; Sperber et al. 2022).

Finally, there is optimism that this line of research will clarify our understanding of lesion syndromes. Suppose we have unprecedented information about the relationship between brain lesions and network dysfunction. In that case, it is reasonable to be hopeful that new insights will emerge regarding the underlying mechanisms of lesion-associated behavioral deficits. This optimistic view is supported in three articles that use insights from disconnectome research to formulate new theoretical insights on brain structure and function. This includes motor awareness (Pacella and Moro 2022) personal neglect (Bertagnoli et al. 2022) and a broad look at the role of networks in understanding brain structure–function relationships (Siegel et al. 2022).

We are grateful to Susan Sesack, Co-Editor-in-Chief of Brain Structure and Function (along with co-editor of this issue, Michel Thiebaut de Schotten), for the opportunity to develop this special issue. We are encouraged by the outstanding contributions of many leaders in the field. It is an exciting time where long-standing questions of the nineteenth and twentieth centuries about how networks contribute to brain function and behavior are becoming increasingly amendable to experimental investigation using imaging tools of the twenty-first century. We are hopeful this special issue will help to increase awareness of the many exciting areas of progress in mapping the disconnectome and uncovering the neural substrates of behavior.

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