

***Disconnectomics: stroke-related disconnection and dysfunction in distributed brain networks***

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## **ABSTRACT (193 words)**

Modern clinical neuroscience was built on observations of how localised damage caused specific functional, cognitive and behavioural deficits. Stroke neurology was a cornerstone of understanding this functional specialisation in the brain. But most lesion-symptom mapping provides little prognostic value above clinical observations. Stroke topography remains a poor indicator of long-term outcome, and with stroke a major risk factor for dementia, there is strong incentive to find markers of predictive value. There is now growing recognition that the damage caused by stroke does not occur in isolation, but is embedded within a complex, highly interconnected, organized and dynamic system: the connectome. Early theories of the widespread effect of focal lesions are resurfacing, buoyed by sophisticated new methods and large-scale data sets. As with all emerging methods and technologies, there may be healthy skepticism as to the appropriateness of the method to the population under investigation or doubt that connectivity derived metrics will ever be clinically translatable. While we acknowledge there remain significant technical challenges to overcome, we argue that the methods provide real potential to illuminate our understanding of the widespread effects and clinical syndromes that can arise from diverse focal damage.

## OPINION (835/800 words)

*“So, Norman, you discovered that neurons have axons. What’s new?” [1]\**

Whilst the terminology may have changed, the concept of connectivity has a long history in our understanding of the remote effects of stroke on the brain. The importance of connections between cortical regions for human cognition was most famously promulgated by Geschwind [2]. Initially proposed by luminaries such as Dejerine, Leipman and Wernicke, in the early part of the twentieth century lesions were only regarded as eloquent if they affected grey matter, prompting Dandy to comment after performing a posterior callosotomy: *“No symptoms follow its division. This simple experiment at once disposes of the extravagant claims to the function of the corpus callosum”* [3]. The concept re-surfaced when Geschwind published his seminal papers in the 1960s, promoting the ‘disconnexion syndrome’ [2]. This term encompasses classical syndromes where lesions to white matter connections or tracts have led to higher cognitive deficits; in contemporary terminology, damage within distributed brain networks resulting in cognitive dysfunction [4]. Geschwind and Kaplan (1962) subsequently described callosal syndromes [5], and paradigmatic syndromes as Dejerine’s alexia without agraphia, and the disconnection aphasia. The study of post-stroke functional deficits also renewed interest in Von Monakow’s concept of diaschisis [6]. He described metabolic depression in sites functionally connected to, but distant from, the infarction, likely the result of deafferentation of excitatory input to the remote region [6]. Modern concepts of diaschisis, termed connectional diaschisis, describe altered structure and function that do not require direct physical connections, but that arise as a result of disconnection in distributed networks.

The connectome, at different spatial and temporal scales, is at the forefront of contemporary neuroscience research [7]. Advances in neuroimaging have further shaped the concept of the disconnection syndrome. Multi-centre studies, clinical trials and research MRI protocols now routinely contain the sequences needed to estimate the synchronous activity of distributed brain regions in functional networks, decipher the brain's wiring, or show patterns in morphology within the complex folding of the cortex. In terms of neuroimaging methods, stroke populations are amongst the most notoriously difficult to study [7]. Stroke creates physical damage that makes it difficult to normalise the brain to a standard template space, an early and important step in analysing data at a group level for both functional and structural connectivity analyses. Estimating the direction of fibre bundles – necessary for structural connectivity studies – becomes difficult in lesioned or perilesional areas where diffusion is changing: more restricted in acute infarcts and more random in the chronic, CSF-filled lesion. In functional neuroimaging, a history of vascular risk factors with concomitant hypoperfusion often precedes stroke, and makes assumptions about the relationship between blood flow and neural activity less tenable [8].

Although these are important caveats, they are technical challenges that do not disqualify the importance of connectivity at a theoretical level. Indeed, much of our conceptualisation of the impact of stroke on the brain, and our strategies for rehabilitation, are implicitly reliant on connectivity to allow brain reorganisation to take place. There may be skepticism that the application of connectomic methods in stroke is just another example of applying the latest techniques, without regard for the appropriateness of the methods to the question, or the population under investigation. It is true that it remains to be seen whether connectomics will have any translational value.

The question remains as to whether connectivity derived metrics will ever translate to the clinic, but it is important to consider the current imaging state of play. We know that, despite decades of research mapping lesion location to observed deficits, imaging alone still does not have predictive power to provide robust prognostic value for stroke deficits or recovery. The same – or very similar – clinical syndromes can arise from lesions of different sizes in different arterial territories, suggesting lesion topography alone cannot predict outcome. Cognitive outcomes are much less predictable than functional outcomes, leaving patients with the uncertainty of a future of long-term cognitive impairment, and even dementia [9]. Siegel and colleagues demonstrated that, while lesion topography is predictive of motor and visual impairment, disruptions to functional connectivity networks better explains impairments in higher order domains such as memory and attention. This finding underpins a neglected assumption in a long history of lesion symptom-mapping, that “the strength of the association between structural damage and behavior is the same irrespective of the behavior that is measured” [10]. Connectomics may provide the bridge between lesion topography and observed clinical syndromes, with disconnection of distributed domain specific networks resulting in domain specific cognitive and functional impairments. It is important not to carry old assumptions with us as we move away from the one-to-one mapping of structure to function. While distributed networks seem to dissociate based on broad functions, these networks are also embedded in complex and dynamic systems [10], made more complicated by the heterogenous nature of stroke and vascular brain burden. Stroke-related *disconnectomics* are unlikely to be understood purely by an examination of physical disconnection, or disruption to synchronous activity, or hypometabolism, or even by remote atrophy, but by consideration of all these complex facets of brain structure and function.

## FOOTNOTE

\* In their seminal 2008 review [1], Catani and Mesulam quote a remarkable neuroscience researcher and colleague of Geschwind's, Jerry Lettvin, as wryly remarking after reading his 1965 paper: "*So, Norman, you discovered that neurons have axons. What's new?*".

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