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Letter: Elucidating the Principles of Brain Network Organisation through Neurosurgery

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Letter: Elucidating the Principles of Brain Network Organization through Neurosurgery

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To the Editor:

The human brain comprises nearly one hundred billion neurons that are highly interconnected and communicate with each other. It is this very interconnectedness that gives rise to functional brain networks that govern complex cognition and human behaviour. To date, the human brain mapping community has largely gleaned insights into the principles of brain network organization from large-scale imaging consortia (i.e. Human Connectome Project) and small-scale observational and interventional studies. We have learned that, in common with other naturally-occurring networks, brain networks demonstrate three topological network features[1]: i) small-worldness, ii) existence of hubs, and iii) community structure. In addition, we have learned that two major driving principles of brain network organization are minimising the energetic costs of wiring whilst investing resources that promote network efficiency[2]. In disease, these principles are stretched from normality, but persist to maintain the classical features of complex networks. Insights into the human connectome have largely been derived from merging neuroimaging with network science, and more recently transcriptomics[3]. However, neurosurgical practice has barely been utilized to unmask the principles of brain network organization. Given that minute (i.e. thalamotomy) to massive (i.e. temporal lobectomy) volumes of brain parenchyma are routinely removed for various clinical indications[4], neurosurgery provides a unique scientific perspective on the human connectome.

Recently, Kliemann and colleagues[5] investigated how functional brain networks were organised in six adults who underwent hemispherectomy (HS) as children. The main objective of their study was to determine how functional brain networks differed between HS patients and controls by quantifying within-network and between-network connectivity. The authors[5] recruited a historical HS cohort with a mean age of 24.33 years. The timing of HS ranged from minutes after birth to early adolescence. Four of the six HS patients underwent complete functional hemispherectomy, while two patients underwent a complete anatomical hemispherectomy. The investigators acquired high-resolution resting-state functional MRI scans and compared the brain’s intrinsic functional architecture between adult HS patients (n = 6) and healthy controls (n = 6). To aid in generalisability, the authors used a normative functional connectome (n = 1482) as a second control dataset. Despite radical surgery, resting-state networks in HS subjects remained in typical configurations with normal levels of within-network connectivity, but increased between-network connectivity. Specifically, they report that the HS cohort had a significantly increased between-network connectivity, outside the range seen in controls, in all seven of Yeo's empirically-derived functional brain networks[6] (i.e. default mode, frontoparietal, etc). Finally, compared to controls, the authors demonstrated that global efficiency (a measure of functional integration) increases and modularity (a measure of functional segregation) remained stable in HS patients.

This study highlights several important findings relevant to the neurosurgical community. First, the authors curated an interesting, hard-to-acquire dataset that provides insight into how large-scale networks organize and communicate when the brain experiences a major physical alteration in early life. They demonstrated that functional brain networks can be reconstructed normally, albeit unilaterally, and that the healthy hemisphere can resume normal function. Second, the authors found normal communication within networks but increased synchronicity between networks, suggesting that HS brains in adulthood work harder to integrate neural activity. The clear implication here is that bilateral hemispheres promote brain network segregation. Third, this study provides weight to using brain stimulation to promote functional remapping and recovery in the contralateral hemisphere after an injury (i.e. stroke)[7] because canonical functional networks can be recapitulated despite highly atypical anatomy. Finally, Kliemann and colleagues[5] imply that following HS in early life, brains undergo compensation to regain function. However, without longitudinal data it is unclear of how these networks topologically reorganise acutely post-surgery and during subsequent rehabilitation. Moreover, it appears that some in the HS cohort were actually hemispheretomies[8,9] and partial bilateral communication could have been preserved despite functional isolation of the healthy hemisphere.

It is important to place the study within a broader neuroscientific context, especially with regards to compensation and network communication. First, on the grounds of this study, there is very little evidence of any kind of reorganisation of brain networks caused by HS, and perhaps the preservation of functional networks is what is surprising. While it is reasonable to assume network plasticity following HS in the developing brain, the authors do not demonstrate this concept due to the absence of longitudinal imaging and cognitive data. The most obvious explanation for their findings is that large-scale functional brain networks are broadly fixed in very early life within their spatial/anatomical configuration to generate internal synchronicity. Moreover, the brain 'switches' the configuration and emphasis of its network communication in response to cognitive demands[10], and thus any form of compensation can only truly be discussed within the framework of task-related activation. Finally, if we interpret increased between-network communication above the normal range as 'compensation', then presumably a priori we would posit that the greater the deviation of activation, the greater the degree of compensation, and thus better cognitive outcomes. While the authors do point out that there was insufficient data to be definitive, the available evidence suggests the opposite; namely, HS patients with the greatest cognitive challenges had increased connectivity across functional networks. Thus, in our cautious view, inferring cognitive "compensation" in the context of network connectivity in a retrospective study needs to be tempered by the available evidence.

In summary, connectomics is still an evolving field of research, although there is reasonable evidence that certain emerging themes may prove to be both reproducible and useful. Neurosurgeons can help elucidate the principles of brain network organisation given the highly distorted anatomy we work with; specifically, predicting surgical morbidity, mechanisms of network plasticity, and the natural history of recovery curves may bi-directionally advance basic neurophysiology and neurosurgical care. Kliemann and colleagues[5] make a positive first step towards these aims with additional studies on the way. Ultimately, we hope neurosurgeons partner with neuroscientists and continue to play an active role in not only deciphering the principles of brain network organisation, but also mechanisms of cerebral plasticity, as there is still much to unravel.

REFERENCES

1. Bullmore E, Sporns O. Complex brain networks: graph theoretical analysis of structural and functional systems. *Nat Rev Neurosci*. 2009;10(3):186-98.
2. Van den heuvel MP, Sporns O. A cross-disorder connectome landscape of brain dysconnectivity. *Nat Rev Neurosci*. 2019;20(7):435-446.

3. Fornito A, Arnatkevičiūtė A, Fulcher BD. Bridging the Gap between Connectome and Transcriptome. *Trends Cogn Sci (Regul Ed)*. 2019;23(1):34-50.
4. Hart MG, Romero-garcia R, Price SJ, Suckling J. Global Effects of Focal Brain Tumors on Functional Complexity and Network Robustness: A Prospective Cohort Study. *Neurosurgery*. 2019;84(6):1201-1213.
5. Kliemann D, Adolphs R, Tyszka JM, et al. Intrinsic Functional Connectivity of the Brain in Adults with a Single Cerebral Hemisphere. *Cell Rep*. 2019;29(8):2398-2407.e4.
6. Yeo BT, Krienen FM, Sepulcre J, et al. The organization of the human cerebral cortex estimated by intrinsic functional connectivity. *J Neurophysiol*. 2011;106(3):1125-65.
7. Kirton A, Chen R, Friefeld S, Gunraj C, Pontigon AM, Deveber G. Contralesional repetitive transcranial magnetic stimulation for chronic hemiparesis in subcortical paediatric stroke: a randomised trial. *Lancet Neurol*. 2008;7(6):507-13.
8. Villemure JG, Mascott CR. Peri-insular hemispherotomy: surgical principles and anatomy. *Neurosurgery*. 1995;37(5):975-81.
9. Kucukyuruk B, Yagmurlu K, Tanriover N, Uzan M, Rhoton AL. Microsurgical anatomy of the white matter tracts in hemispherotomy. *Neurosurgery*. 2014;10 Suppl 2:305-24.
10. Bertolero MA, Yeo BTT, Bassett DS, D'esposito M. A mechanistic model of connector hubs, modularity and cognition. *Nat Hum Behav*. 2018;2(10):765-777.