Editorial Commentary

Stability and plasticity of functional brain networks after hemispherectomy: implications for consciousness research

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Cerebral hemispherectomy, or surgical removal of an entire hemisphere of the brain, is performed in cases of severe and intractable epilepsy (1). Surprisingly, despite deficits including hemiparesis and hemianopsia post-surgery, patients are often able to recover a remarkable degree of cognitive and sensorimotor function in the long term using the remaining hemisphere (2-4). The neural plasticity that underlies this functional recovery is a topic of ongoing investigation in clinical neuroscience. A considerable neuroimaging literature has accumulated documenting visual, motor, and language function in hemispherectomy patients using task-based functional magnetic resonance imaging (fMRI), revealing compensatory patterns of activity in the preserved hemisphere of these individuals (5-7). Far less is known about the integrity of large-scale functional brain networks and their potential for reorganization after this drastic surgery. Kliemann and colleagues collected resting state fMRI data from six high-functioning adults who had undergone either anatomical or functional hemispherectomy as children (8). Anatomical hemispherectomy is a surgical procedure in which the affected hemisphere, often including subcortical structures, is entirely or nearly entirely removed. Functional hemispherectomy is a procedure in which the affected hemisphere is isolated by severing all connections to the functional hemisphere. Two of the patients studied by Kliemann and colleagues had undergone left hemispherectomy, and the remaining four had undergone right hemispherectomy.

An innovation of the study design was the inclusion of two healthy control cohorts for comparison. The first control cohort included six individuals matched on demographic variables who were scanned at the same facility as the hemispherectomy patients using similar MRI data acquisition parameters. The second control cohort consisted of 1,482 participants from the publicly available dataset known as the Brain Genomics Superstruct Project (GSP, https://www.neuroinfo.org/gsp/). Another strength of the study was the use of surface-based registration, an approach more sensitive to individual anatomy, for analyzing the resting state fMRI datasets. In a series of elegant analyses, the authors first tested whether whole-brain parcellation derived from healthy control data could be successfully applied to hemispherectomy patients, then tested the reliability of functional connectomes derived from two separate scanning sessions from each individual,

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and finally assessed commonalities and differences between functional networks observed in a single hemisphere of patients compared with those computed from a single hemisphere of control participants.

The authors started with a validated, widely-used 7-network parcellation scheme (9) that has been further subdivided to obtain a finer resolution (10). Using this scheme resulting in 200 brain parcels per hemisphere, the authors found evidence for within-parcel homogeneity in hemispherectomy patients. This proof-of-principle analysis suggests that a parcellation scheme derived from individuals with two intact hemispheres can be applied to subdivide brains with markedly diverging anatomy such as those of hemispherectomy patients.

Another innovation of the study by Kliemann and colleagues was the use of functional connectome fingerprinting (11) to assess the reliability of functional connectivity profiles using fMRI data collected on two separate occasions from the same individuals. These analyses showed that for the majority of hemispherectomy patients and control participants (5 out of 6 in both cases), as well as the majority of individuals from the GSP dataset, connectome fingerprinting was successful. This means that the functional connectome of the brain was stable and discriminative (e.g., able to identify specific individuals) for the majority of datasets examined.

The main test of functional network integrity in hemispherectomy patients was the comparison of within- and between-network functional connectivity with similar metrics derived from control participants. Surprisingly, within-network intrahemispheric functional connectivity was found to be relatively comparable across the hemispherectomy and two control cohorts using multiple analytic strategies. When comparing between-network functional connectivity across groups, those with hemispherectomy exhibited markedly higher connectivity compared with both control cohorts. This means that connectivity between brain parcels belonging to separate networks was higher than expected in individuals who had undergone hemispherectomy, a finding that held for nearly all large-scale networks examined. Of note, the stronger between-network connectivity result in individuals with hemispherectomy was most pronounced for somatosensory/motor and visual networks.

One particularly interesting aspect of the hemispherectomy patients was that for some of these individuals, the negative correlation typically observed between default mode and attention networks (12) was reduced. Finally, using graph theoretical analyses, the authors found that global efficiency (the average inverse shortest path length in a network) and modularity (the degree to which the overall network can be subdivided into groups of nodes) was intact, and even relatively high, in some hemispherectomy patients.

This study represents the most comprehensive investigation to date of whole-brain functional connectivity and network integrity in hemispherectomy patients. The authors employed state-of-the-art analytic tools and insights from network neuroscience (13,14) to explore brain network properties in a relatively large group of patients, and compared these metrics to well-characterized samples of neurotypical individuals. Perhaps the most surprising conclusion to take away from this study is just how few differences in functional network connectivity were observed in these patients who have undergone drastic neurosurgery. The authors interpret the finding of higher between-network functional connectivity in hemispherectomy patients as reflecting adaptive increases in network integration as a compensatory mechanism to support cognitive functioning (8).

The most pressing follow-up question from this study is: how does functional network reorganization support cognition and behavior in these individuals? While the small sample size did not permit robust analyses to address this question, the authors did find hints of relationships between network metrics and social responsiveness, IQ, and psychomotor function in the patients examined. It will be important for future work to determine how individual differences in functional network connectivity relate to functional outcomes in patients. The ideal scenario would involve longitudinal studies in which neuroimaging data are collected both pre- and post-surgery. This would permit tracking of within-subject changes in functional network connectivity as a result of the surgery, and could be used to directly assess how plasticity and network reorganization post-hemispherectomy supports preservation of function. If a large database of longitudinal data were to become available, this could also ultimately be used to develop machine learning algorithms designed to predict functional outcomes from pre-surgery neuroimaging data, thus aiding clinicians in determining prognosis.

One caveat to keep in mind is that the sample of hemispherectomy patients was quite heterogeneous in several respects. While the age range of participants was narrow (20–31 years), the sample included four females and two males, of whom four were right handed and two were left handed. Other sources of heterogeneity within the sample were age at seizure onset (birth to 10 years), age at hemispherectomy (3 months to 11 years), differences in etiology (perinatal stroke, Rasmussen encephalitis, and cortical dysplasia), and the fact that two patients had undergone anatomical hemispherectomy surgeries while four had undergone functional hemispherectomy. Finally, two of the patients had left hemispherectomy, and the remaining four had right hemispherectomy. For higher cognitive functions such as language that are typically left-hemisphere dominant in right-handed individuals, one might expect to see hemispheric differences in brain activation and connectivity within specific networks subserving these functions.

There are still several unknowns surrounding the issues of optimal developmental stage at which to perform hemispherectomy, and recovery of function post-surgery. Neuroimaging data from much larger samples will be necessary to further explore the question of how functional network reorganization post-hemispherectomy varies as a function of age of surgery, etiology, and handedness. In addition, future work directly comparing left vs. right hemispherectomy patients will be necessary to understand the malleability of hemispheric specialization for specific high-level cognitive functions such as language (15).

One of the most interesting aspects of the hemispherectomy phenomenon is briefly mentioned by the authors. Individuals who have undergone hemispherectomy can still report intact conscious experiences despite loss of a large percentage of their brains (16). This presents a conundrum for influential theories of consciousness such as the global neuronal workspace (GNW) hypothesis, which postulates that conscious access results from a non-linear network ignition associated with recurrent processing that amplifies and sustains a neural representation, allowing the information to be globally accessed. A central tenet of this hypothesis is that conscious processing relies on recurrent loops between distributed processors in the brain (17). While interhemispheric connectivity and hemispheric specialization are not explicitly discussed in the context of GNW, a theory postulating that whole-brain dynamics underlie conscious experience might struggle to account for the phenomenon of preserved consciousness in hemispherectomy, where only one cerebral hemisphere is available to maintain consciousness. This raises the question of whether it is possible that separate GNWs, and consequently separate consciousnesses, can form independently within each hemisphere. The finding of greater between-network connectivity in hemispherectomy reported by Kliemann and colleagues could also provide insight into how consciousness is supported when less neural real estate is available.

Roger Sperry, who won the Nobel Prize in physiology and medicine in 1981, had much to say on the topic of the unity of consciousness from a phenomenological perspective. Findings from studies of split-brain patients demonstrate that these individuals also exhibit evidence of remarkably intact functional networks, cognitive abilities, and conscious experiences despite lacking all major connections between the two cerebral hemispheres (18-21). Sperry's accounts of individuals who have undergone commissurotomy detail that "*the general behavior and conversation during the course of a casual social encounter without special tests typically reveals nothing to suggest that these people are not essentially the same persons that they were before the surgery with the same inner selves and personalities*". He goes on to note, however, that "*despite the outwardly seeming normality… and the apparent unity and coherence of the behavior and personality of these individuals, controlled lateralized testing for the function of each hemisphere independently indicates that in reality these people live with two largely separate left and right domains of inner conscious awareness*" and that "*… each surgical disconnected hemisphere appears to have a mind of its own, each capable of controlling the behavior of the body but each cut off from, and oblivious of, conscious events in the partner hemisphere*" (22). Extrapolating from this split-brain research, we can speculate that the intact consciousness exhibited by patients who have undergone hemispherectomy may be due to the fact that the two cerebral hemispheres were independently capable of supporting consciousness to begin with. The study of hemispherectomy thus provides a unique opportunity for empirical investigation of questions surrounding the unity of consciousness. Future work exploring consciousness in hemispherectomy patients will undoubtedly provide exciting avenues for collaboration between physicians, neuroscientists, and philosophers.

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Footnote

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