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# Cognitive eloquence in neurosurgery: Insight from graph theoretical analysis of complex brain networks

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ABSTRACT

The structure and function of the brain can be described by complex network models, and the topological properties of these models can be quantified by graph theoretical analysis. This has given insight into brain regions, known as hubs, which are critical for integrative functioning and information transfer, both fundamental aspects of cognition. In this manuscript a hypothesis is put forward for the concept of cognitive eloquence in neurosurgery; that is regions (cortical, subcortical and white matter) of the brain which may not necessarily have readily identifiable neurological function, but if injured may result in disproportionate cognitive morbidity. To this end, the effects of neurosurgical resection on cognition is reviewed and an overview of the role of complex network analysis in the understanding of brain structure and function is provided. The literature describing network, behavioral, and cognitive effects resulting from lesions to, and disconnections of, centralized hub regions will be emphasized as evidence for the espousal of the concept of cognitive eloquence.



## Introduction

The concept of eloquence in neurosurgery is classically defined as regions of the brain that are involved in readily identifiable neurological function, and if injured, result in disabling neurological deficit [1]. However, this definition does not account for regions critical for implementing higher cognitive functions, which are increasingly being recognized as being important for quality of life in neurosurgical patients [2]. It has long been held that functional segregation and integration are fundamental principles of cortical organization [3]. Not surprisingly then, mounting evidence suggests that integrative and dynamic processes across distributed regions play a role in virtually all cognitive domains [4–6]. Furthermore, focal lesions may result in unexpected or widespread deficits that are not predicted by the local functional properties of the area [7]. By modelling the structure and function of the brain through application of graph theoretic principles [8–10], the burgeoning field of connectomics [11] has provided evidence for the existence of brain regions critical for these integrative functions. These regions, classified as hubs, have a central placement in the overall network structure of the brain and represent focal points of convergence and divergence of specialized neural information [12–17]. Lesions to hubs have been shown to result in pronounced effects on behavioral and cognitive functioning [18], and computational models show that disruption of hub nodes and edges have dramatic effect on overall network organization and function [19–21]. Interestingly, brain hubs are principally located in multimodal association areas, often associated with higher cognitive function [22,23]. In this manuscript the concept of 'cognitive eloquence' will be proposed; that is, regions (cortical, subcortical and white matter) of the brain which may not necessarily have readily identifiable neurological function, but if injured during surgery, may result in disproportionate cognitive morbidity. In this respect, the literature describing the result of resective surgery on cognitive ability will be reviewed, and an overview of the role of complex network analysis in the understanding of brain structure and function will be provided. The literature describing network, behavioral, and cognitive effects resulting from lesions to, and disconnections of, centralized hub regions will be emphasized as evidence for the espousal of the concept of cognitive eloquence in neurosurgery.

## Resective surgery and cognition

The earlier detection of gliomas [24] and improved survival [25–27] with modern treatment regimes, has led to increasing emphasis on the maintenance of quality of life for brain tumour patients. Quality of life is dependent on neuropsychological

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function and even minor cognitive deficits may negatively affect health related quality of life [2] and return to professional activity [28]. Neurocognitive outcome is dependent on multiple factors, including pre-morbid function, tumor effects and recurrence, epilepsy and anti-epileptic drugs, as well as the specifics of oncological treatment [29]. Whole brain radiation is a well-known cause of post-treatment neurocognitive deficits. However, the evidence regarding the effect of surgical resection on neurocognitive function is scarce and conflicting. While improvement from baseline is possible [30–32], many studies have shown worsening of multiple cognitive domains [33–37]. For example, attentional deficits are seen after frontal or prefrontal tumour resections [31,38,39], fronto-orbital resections can severely impair executive functioning in a reward learning task [36], and impaired virtual planning of real life activities is shown after resections in left and right pre-frontal cortex [35]. Wu et al. [33] attempted to isolate the effect of surgery on neurocognitive function for insular gliomas. Both the insular glioma and control glioma groups had similar neurocognitive impairments before surgery, with the insular glioma group showing significantly worse performance on naming tasks. Post-operatively, both groups had decline in most neurocognitive domains, with a trend towards greater decline in learning and memory in the insular glioma group. While the authors concluded that insular gliomas could be removed without profound neurological or cognitive morbidity, it is more important to note that both groups demonstrated neurocognitive decline suggesting neurocognitive morbidity is common after resection for brain tumours in a variety of locations. Social cognitive functions, such as theory of mind ability, emotion recognition, and empathy can also be affected by surgery to the prefrontal cortex [40]. For example, in a study of 31 patients who had undergone unilateral right and left frontal lobe excision for a variety of lesions, significant impairments in theory of mind ability were found relative to a control group [41]. These deficits were found to be independent of deficits in tests of executive functions suggesting that different functional networks subserve these diverse functions. Social behavior and emotional deficits have also been found after surgical lesions to the orbitofrontal cortex and the anterior cingulate cortex [42]. In an insightful case report, a patient with a left frontal lobectomy for a low grade glioma demonstrated marked dissociation between his performance on standard neuropsychological tests and his everyday behavior. While no specific deficits were seen on neuropsychological testing, the patient was markedly impaired on the Multiple Errands task, which required him to operate in relatively unpredictable pedestrian environments. The patient had difficulty responding to social cues, was less efficient and made more errors, frequently broke rules of the test, demonstrated disinhibited behavior, and misinterpreted tasks [43]. This points to the need for more ecologically valid assessments of executive dysfunction and functional capacity, such as testing patients in virtual reality simulators [44]. Cognitive impairment in epilepsy is also a major concern for patients and clinicians [45], though estimating the effects of surgical resection on cognitive functioning has proven to be difficult [46]. A wide variability in the effects of epilepsy surgery, ranging from cognitive improvement to cognitive decline has been observed [47,46,48]. Cognitive functioning after epilepsy surgery is related to pre-operative function, patient demographic characteristics, functional adequacy of the tissue to be resected, and surgery specific factors such as side of surgery and extent of resection [47,48]. Memory and language deficits are most commonly seen after temporal lobe resections [49], while post-operative decline in a variety of cognitive functions are seen after extra-temporal resections. For example, resection of the dorsolateral prefrontal cortex can lead to working memory and multi-tasking deficits [50], while resections in the parietal lobe can lead to anomia, agraphia, alexia, apraxia, acalculia [51,52] and declines in non-verbal IQ [53]. Patients undergoing resection of the insular cortex for epilepsy have been shown to demonstrate impairments in emotion recognition and empathy [54]. While the true incidence of neurocognitive deficits following resection is unknown, it is clear that neurosurgical patients can experience significant cognitive morbidity [55,45] and neurosurgeons should attempt to minimize the effect of surgery.

## Graph theory and complex network analysis

The origin of the mathematical field of graph theory has its roots in 1736 [56], where the notion of representing an interconnected system as nodes and edges was first proposed. The resulting mathematical structure is called a graph and graph topology is the quantitative description of the relationships between nodes and edges. The brain can be described as a complex network where sets of discrete neural elements (nodes) are linked (edges), and the topology of these networks can be quantified by graph theoretical analysis (Fig. 1).

### *Structural vs functional connectivity*

Brain connectivity can be separated into structural, functional, and effective connectivity where important distinctions are made between the resulting networks [57,58]. The conceptualization of structural brain networks is relatively straight-forward, where neurons or brain regions (nodes) are linked by edges representing physical connections (synapses or axonal projections). In contrast, functional networks are characterized by brain regions that demonstrate synchronized spontaneous activity that does not necessarily correspond with direct neuronal communication. Thus, edges in a functional network are not represented by a specific anatomical connection but instead represent signalling and communication events that unfold within the underlying structural network [15]. In effective connectivity networks, edges represent direct or indirect causal influences of one region on another [59]. Attempts to map the structural connectivity of the brain use diffusion tensor imaging or diffusion spectrum imaging. Mapping of the functional connectivity of the brain is performed by resting-state functional MRI (rs-fMRI), magnetoencephalography (MEG), electroencephalography (EEG) or multi-electrode array (MEA) data.

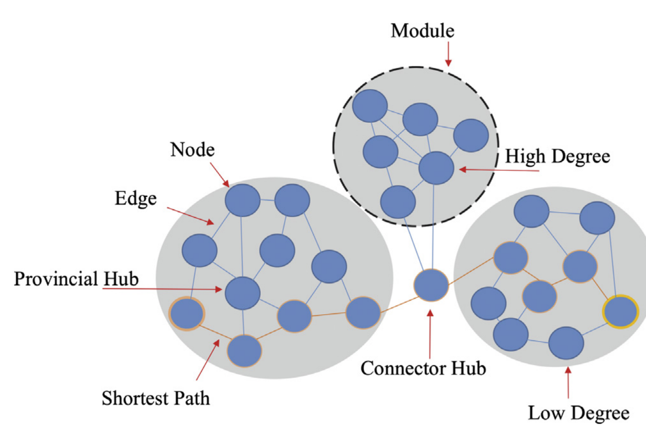


**Fig. 1.** Graph measures. An example of a simple, unweighted, binary graph demonstrating key network measures. Three modules are demonstrated as clusters of nodes and edges. Orange line represents the shortest path between two modules. Provincial hub determined by high degree within a module. Connector hub demonstrates high centrality, shown here by high participation coefficient (diverse intermodular connections) and betweenness centrality (involved in a high number of shortest paths across the network). Nodes with high centrality are hypothesized to represent regions of cognitive eloquence as argued in the manuscript.