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CLINICAL STUDY

# Unexpected hubness: a proof-of-concept study of the human connectome using pagerank centrality and implications for intracerebral neurosurgery

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## Abstract

**Introduction** Understanding the human connectome by parcellations allows neurosurgeons to foretell the potential effects of lesioning parts of the brain during intracerebral surgery. However, it is unclear whether there exist variations among individuals such that brain regions that are thought to be dispensable may serve as important networking hubs.

**Methods** We obtained diffusion neuroimaging data from two healthy cohorts (OpenNeuro and SchizConnect) and applied a parcellation scheme to them. We ranked the parcellations on average using PageRank centrality in each cohort. Using the OpenNeuro cohort, we focused on parcellations in the lower 50% ranking that displayed top quartile ranking at the individual level. We then queried whether these select parcellations with over 3% prevalence would be reproducible in the same manner in the SchizConnect cohort.

**Results** In the OpenNeuro (n = 68) and SchizConnect cohort (n = 195), there were 27.9% and 43.1% of parcellations, respectively, in the lower half of all ranks that displayed top quartile ranks. We noted three outstanding parcellations (L_V6, L_a10p, and L_7PL) in the OpenNeuro cohort that also appeared in the SchizConnect cohort. In the larger Schizconnect cohort, L_V6, L_a10p, and L_7PL had unexpected hubness in 3.08%, 5.13%, and 8.21% of subjects, respectively.

**Conclusions** We demonstrated that lowly-ranked parcellations may serve as important hubs in a subset of individuals, highlighting the importance of studying parcellation ranks at the personalized level in planning supratentorial neurosurgery.

**Keywords** Unexpected hubness · Centrality · Hubs · Connectome · Connectomics

## Abbreviations

| | |
|---|---|
| DVAR | Spatial standard deviation of successive difference images |
| ROI | Regions of interest |
| HCP | Human connectome project |
| SFL | Superior frontal lobe |
| TE1p | Posterior portions of the middle and inferior temporal gyrus |
| TGd | Temporal gyrus dorsal |

## Introduction

Eloquence is traditionally regarded as one of the most important considerations in intracerebral neurosurgery [1, 2]. The transgression of a neurologically eloquent area will result in undesired clinical outcomes and alteration of neurological functions [3]. The study of the human connectome aims to shed light on brain functions in the context of a network, in which areas of the brain are interconnected to deliver higher cerebral functions [4]. The assumption that measurements of centrality are identical among all individuals in the current era of personalized medicine can be hazardous in the context of neurosurgical interventions. It is still unclear why some patients develop more cognitive impairments after tumor resection surgeries in "non-eloquent" areas than others,

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suggesting that individual variations in cerebral eloquence may be present [5].

Diffusion tractography, which highlights connections among different areas of the brain, provides major insights into the human connectome [6, 7]. DTI, along with fMRI, has allowed for safer and more controlled surgical resections of gliomas [8–10]. The common use of DTI for surgical planning is largely based on the goals of preserving obvious neurological functions, such as speech and motor function. However, the limitation of DTI lies in the fact that its interpretation is based on presumed important anatomical regions, based largely on our understanding of Brodmann classifications, such as Areas 44 and 45 (Broca's area) or Area 4 (Motor cortex) [11]. Recently, our group utilized PageRank Centrality to predict regions of eloquence and we found that high PageRank centrality corresponded well with areas that were traditionally thought to be "no-go" zones for neurosurgeons [1]. Our previous results noted that there were anatomical differences in centrality among individuals [1]. As routine DTI information is only useful for correlating with obvious neurological functions, it has limited value in illustrating areas of eloquence that are more related to cognition and other neuropsychological measures. This is further compounded by the fact that there exist innate anatomical differences among individuals such that we need a new method to identify potential areas in the brain that, if transgressed, may have unexpected neuropsychological consequences.

In this study, we leveraged two large cohorts of subjects who have undergone diffusion neural imaging. We utilized our proprietary artificial intelligence software to determine the ranks of different regions of interests (ROIs). Our goal is to examine the approximate prevalence of unexpected high ranks or "hubness", in areas that are commonly inferred to have low importance or ranks. We then describe these areas in the anatomical context and discuss their potential implications for intracerebral neurosurgery.

## Methods

### Data collection

Magnetic resonance images consisting of diffusion tensor images from two cohorts of healthy subjects, OpenNeuro (https://openneuro.org) and SchizConnect, were parcellated into ROIs [12, 13]. The diffusion tensor images (DTIs) were processed using the Omniscient software (https://www.o8t.com), which employs a standard processing steps in the Python language which specifically include the following steps: (1) the diffusion image is resliced to ensure isotropic voxels, (2) motion correction is performed using a rigid body alignment, (2) slices with excess movement (defined as DVARS > 2 sigma from the mean slice) are eliminated, (3) the T1 image is skull stripped using a convolutional neural net (CNN), this is inverted and aligned to the DT image using a rigid alignment, which is then used as a mask to skull strip the DT, (4) gradient distortion correction is performed using a diffeomorphic warping method which aims to locally similarize the DT and T1 images, (5) eddy current correction is performed, (6) Fiber response function is estimated and the diffusion tensors are calculated using constrained spherical deconvolution, and (7) deterministic tractography is performed with random seeding, usually creating about 300,000 streamlines per brain.

Subjects whose scans contained artifacts, poor field of view, inadequate slices, and other general faults in the scans were removed from the dataset. Nodal centrality measures using PageRank Centrality were determined as previously described [1]. PageRank score ranged from 1 to 379, with a higher score predicting the degree of eloquence.

### Creation of a personalized brain atlas using machine learning-based parcellations

The Omniscient software creates a machine learning-based, subject-specific version of the Human Connectome Project (HCP) Multi-Model Parcellation version 1.0. The HCP atlas based on diffusion tractography structural connectivity [14]. The general concept is to use a machine learning-based technique for parcellating a brain, avoiding the limitations of assigning brain voxels to parcellations by using structural connectivity instead of anatomic-based methods.

We trained a machine learning model using the subject specific version of the HCP atlas based on diffusion tractography structural connectivity [5]. This method was created by training a model on 200 normal subjects by first, processing T1 and DT images as described above. A HCP atlas in NIFTI MNI space was then warped onto each brain and the structural connectivity was calculated between every pair of this atlas and a set of Regions of Interest (ROIs), which contained 8 subcortical structures per hemisphere and the brainstem, based on the streamlines which terminated within an ROI. This step both allows the generation of feature vectors (a voxel to parcellation structural connectivity matrix) and generates a centroid of the parcellation, which is utilized to constrain the voxels studied for assignment of a given parcellation to a plausible area in the vicinity of its typical position. The feature vectors for each region were then used as a training set to fit a gradient boosted tree-based model using XGBoost. We used Xgboost for three reasons. (1) It is computationally effective—the X in the algorithm stands for Extreme and relates to the highly parallelised approach of this algorithm. (2) It deals with many different flavours of data, in this case non-linear and discrete observations (number of tracts between parcellation x and y). (3) It provided

the best performance on training with tenfold cross validation (data not shown). To ensure clinical relevance of the model we optimized the algorithm on precision.

This model is then used to classify held out subject parcellations by warping the HCP atlas to the new brain and collecting a set of feature vectors of the connectivity of each voxel based on this first pass. The feature vectors are then used to determine each voxel parcellation identity. Our method transforms an atlas onto a brain and calculates the structural connectivity between every pair of the applied atlas and a set of regions of interest, allowing generation of feature vectors and parcellation centroid to determine each voxel parcellation identity (data not shown).

### Data analysis

Regions of interest in the form of parcellations of each subject were ranked. Considering the goal of examining regions of eloquence in areas that are otherwise thought to low nodal functions, we focused on parcellations that were in the lower half of the rank list relative to the median (1–190). In these parcellations, we attempted to identify individual subjects that displayed high nodal centrality, defined as the highest quartile of ranks (285–379). We empirically focused these parcellations that occurred more than 3% of the OpenNeuro cohort and identified those that appeared in the same fashion in the SchizConnect cohort. We utilized the Omniscient software to localize these parcellations. Unexpected hubness, therefore, is defined as parcellations that are of low importance on average but, in certain individuals, display high importance.

## Results

### The validity of our parcellation scheme

We performed parcellations of individuals from two different cohorts involving healthy subjects. We observed the top-ranking ROIs in each cohort and queried whether they were of anatomical significance (Table 1). We noted that all of the areas in the top-10 ranking ROIs were considered as eloquent areas and resembled previously observed findings using the HCP cohort [14]. All of the top-ranking ROIs are all anatomical regions of eloquence, as previously described [14].

### Prevalence of unexpected hubness

In the OpenNeuro cohort (n = 68 subjects), there were 53 (27.9%) parcellations in the lower half of all ranks (n = 190) that displayed top quartile ranks (red as opposed to blue in Fig. 1a). The number of subjects displaying these outlying parcellations ranged from 1 to 6 (range 1.47 to 8.82%, mean 2.83 ± 0.26%). In the SchizConnect cohort (n = 195 subjects), there were 84 (43.1%) parcellations in the lower half of all ranks (n = 190) that displayed top quartile ranks (Fig. 1a). The number of subjects displaying these outlying parcellations ranged from 1 to 20 (range 0.51 to 10.26%, mean 2.29 ± 0.23%).

We decided to focus on parcellations that had unexpected hubness at or above the prevalence of 3% of all subjects. We noted three outstanding parcellations in the OpenNeuro cohort that also appeared in the SchizConnect cohort (Fig. 1b). These parcellations were L_V6 (Fig. 2), L_a10p (Fig. 3), and L_7PL (Fig. 4) at a prevalence of 4.41, 8.82, and 7.35%, respectively in the OpenNeuro Cohort. In the larger Schizconnect cohort, L_V6, L_a10p, and L_7PL had unexpected hubness in 3.08%, 5.13%, and 8.21% of subjects, respectively.

**Table 1** Top 10 Highest ranked ROIs in Open neuro and Schiz connect cohorts

| Ranks (out of 379) | Open neuro (n = 68) | Schiz connect (n = 190) |
|---|---|---|
| 1 | Brainstem | Brainstem |
| 2 | R_Cerebellum | R_Cerebellum |
| 3 | R_Thalamus | L_Cerebellum |
| 4 | L_Thalamus | L_Thalamus |
| 5 | L_VentralDC | L_TE1p |
| 6 | L_Cerebellum | R_Thalamus |
| 7 | R_VentralDC | R_TGd |
| 8 | L_SFL | L_V2 |
| 9 | L_TE1p | R_V1 |
| 10 | L_TGd | L_VentralDC |

### Anatomical correlations of unexpected hubs

#### Left visual area 6 (L_V6)

Area V6 (visual area 6) is part of the superior, vertically-oriented areas of the occipital lobe in the anterosuperior portion of the cuneus [15]. It is structurally connected to the IFOF, middle longitudinal fasciculus (MdLF), and forceps major (FM). IFOF projections terminate at parcellations in the frontal lobe including 9a, 9p, 9m, and 8BL. The MdLF runs parallel to the IFOF then courses laterally to the superior temporal gyrus, as the IFOF courses medially between the lateral ventricle and insula. It has been implicated in the processing and analysis of visual motion and has been demonstrated in lesion studies to cause motion blindness and other motion-related visual disturbances [16].

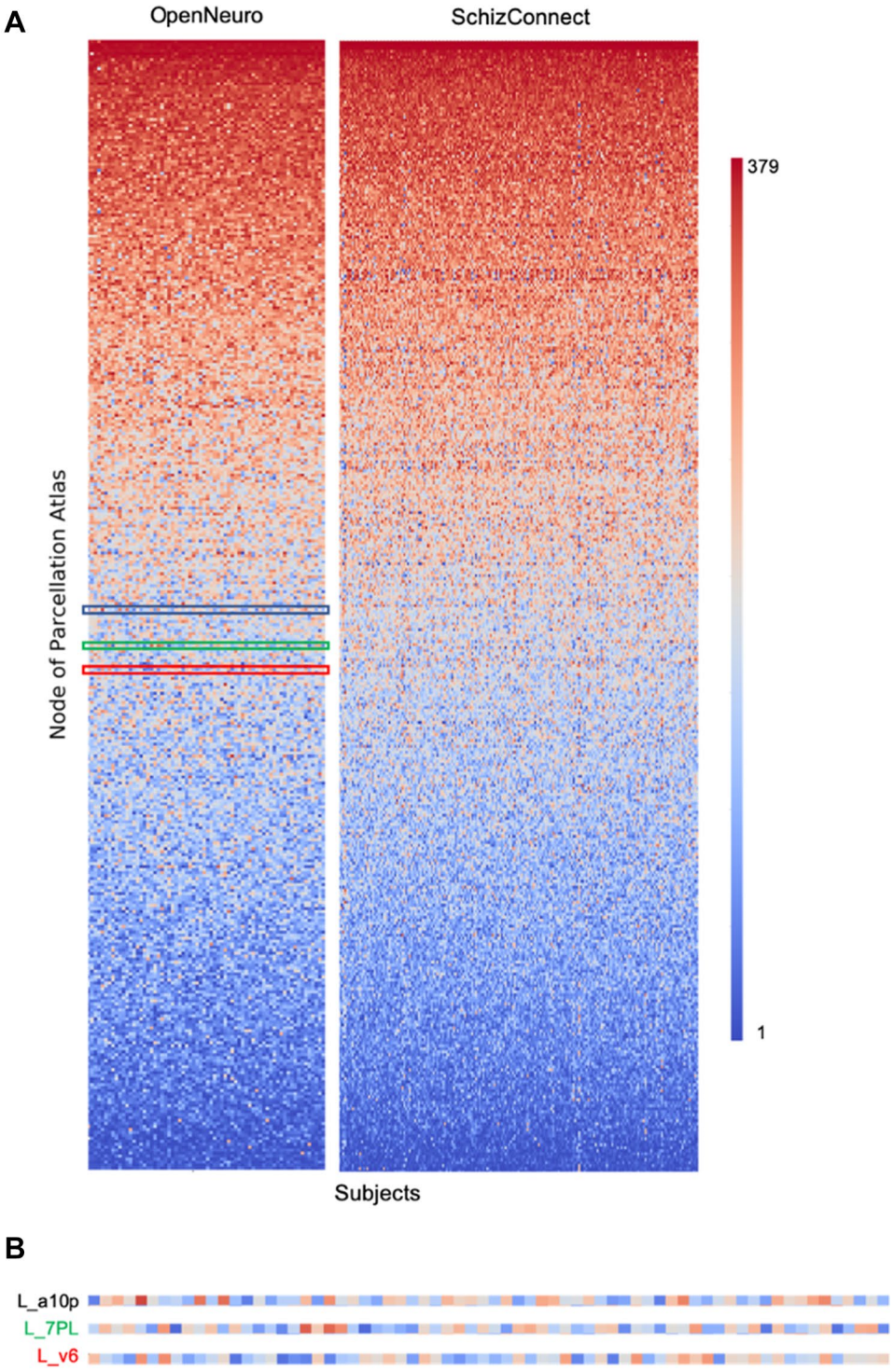


**Fig. 1** PageRank order of two cohorts and unexpected hubness. **a** Heatmap of parcellations ordered by PageRank centrality from 1 to 379. **b** Parcellations that demonstrate unexpected hubness in Open Neuro cohort that are reproduced in the Schiz Connect cohort (color corresponds with brackets in the heatmap). Red is high and blue is low ranking

### Left anterior 10 polar (L_a10p)

Area a10p (anterior 10 polar) is located at the fusiform junction of the anterior-most aspects of the superior and middle frontal gyri [17]. It is structurally connected to the IFOF and contralateral hemisphere. Contralateral connections travel through the genu of the corpus callosum with the forceps minor to end at 9a and p10p. Area a10p is involved in episodic and working memory tasks. Brodmann area 10 more generally is activated with the increasing complexity of working memory tasks [18]. This area also plays a role in abstract cognitive function [19].

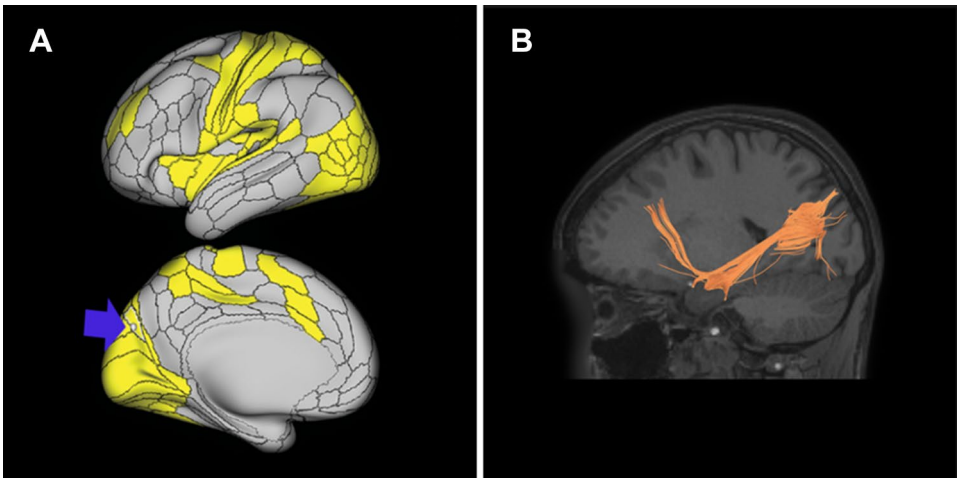


**Fig. 2** **a** Lateral-medial view of Left V6 parcellation. It is a vertically oriented area in the anterosuperior portion of the cuneus, just posterior to the superior parieto-occipital sulcus. **b** DTI illustration of L_V6 and its connections (areas 1, 2, 3a, 3b in the sensory strip, area 4 in the motor strip, areas SCEF, FEF in the premotor region, areas 9-46d, and 46 in the lateral frontal lobe, areas a24prime, and p32prime, 5mv, 23c in the medial frontal lobe, areas FOP1, FOP3, FOP4, OP4, OP2-3, 43, PFcm, STV, PoI1, PoI2, MI, RI, TA2, 52, A4, MBelt, and PBelt in the insula opercular regions, areas 7PC, 7AL, 7am, VIP, LIPv, PGp, PFop, IPS1, IP0, PCV, and DVT in the parietal lobe, areas ProS, V1, V2, V3, and V4 in the medial occipital lobe, areas V3a, V3b, V7, and V6a of the dorsal visual stream, areas FFC, VVC, V8, VMV1, VMV2, and VMV3 of the ventral visual stream, and areas TPOJ2, TPOJ3, V3cd, V4t, LO1, LO2, LO3, MT, MST, PH, and FST of the lateral occipital lobe.)

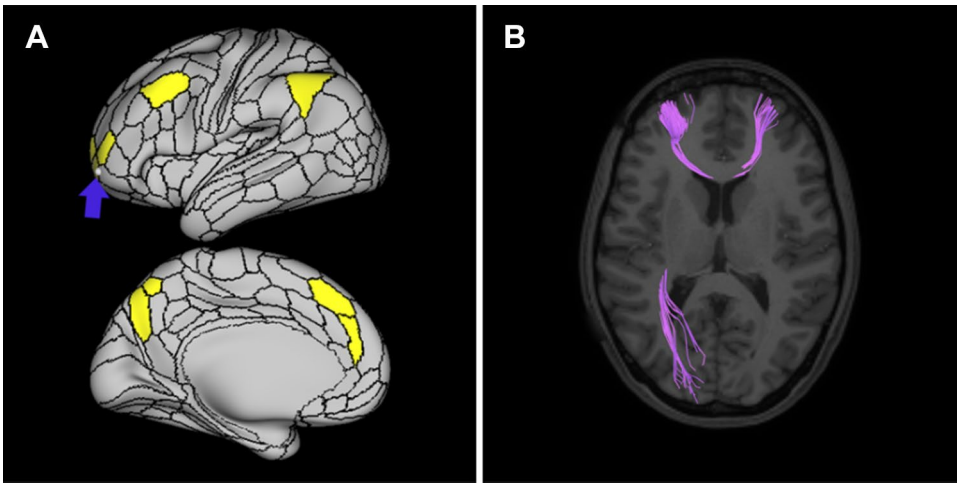


**Fig. 3** **a** Lateral-medial view of Left a10p parcellation. It is located at the fusiform junction of the anterior most aspects of the superior and middle frontal gyri. **b** DTI illustration of L_a10p and its connections (IFOF and contralateral hemisphere. Contralateral connections travel through the genu of the corpus callosum with the forceps minor to end at 9a and p10p. IFOF connections travel from a10p through the extreme/external capsule and continue posteriorly to end at occipital lobe parcellations V1, V2, V3, V6 and V6a. Local short association bundles are connected to 10d, 10pp, p10p, a9-46v and 9-46d

### Left Area 7 posterior-lateral (L_7PL)

Area 7 posterior-lateral is found on the posterior superior surface of the superior parietal lobule [20]. It is structurally connected to the IFOF, thalamus, MdLF, and local parcellations. The function of area 7PL in the left and right hemispheres is distinct [21]. In the left hemisphere, this region is involved in vision motion, space, vision shape, attention, and working memory. It may also be involved in episodic memory retrieval and saccade-related activity [22].

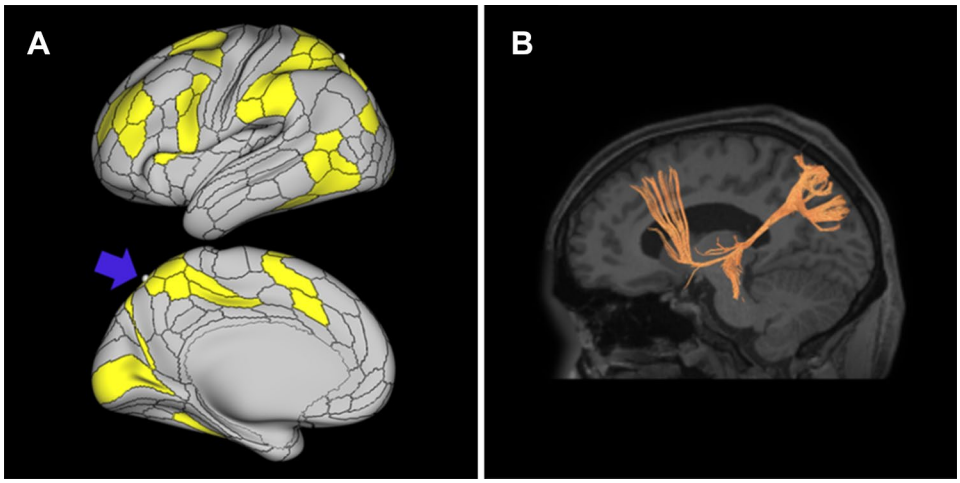


**Fig. 4** **a** Lateral-medial view of Left 7PL parcellation. It is located on the posterior superior surface of the superior parietal lobule. **b** DTI illustration of L_7PL and its connections. 7PL is structurally connected to the IFOF, thalamus, MdLF and local parcellations

## Discussion

The idea of eloquence is a critical concept in neurosurgery in determining which areas of the brain we can transgress without resulting in major neurological consequences. The Spetzler-Martin system is the classic, well-adopted model of brain eloquence for surgical resection of arteriovenous malformation [2]. The utilization of this paradigm assumes that there is high homogeneity among individuals. This current study was not aimed to redefine the concept of eloquence but raise the possibility that eloquence could vary among individuals and that individuals could have eloquent regions that are not speech- or motor-related functions but are cognitively essential. In this proof-of-concept study, we evaluated the importance of each brain parcellation by PageRank and attempted to query parcellations that may exhibit a high degree of hubness despite being "non-eloquent" on average.

### Are there parcellations in the brain that are unexpectedly important hubs?

As we venture into individualized neurosurgical planning using parcellation schemes applied to DTI studies, we question whether all parcellations display similar importance or hubness among individuals. We derived a simple, empiric scheme and looked at the prevalence of parcellations that displayed high ranks (top quartile) in subjects despite being in the lower half of centrality ranking in our cohorts. In the three parcellations that we identified in the OpenNeuro cohort that was also reproduced using the SchizConnect cohort, unexpected hubs could be present in as high as eight percent of individuals, suggested that an otherwise negligible parcellation such as L_7PL can potentially be functionally important in approximately one out of 12 people, a proportion that is not insignificant. Even a parcellation such as L_V6 that can be unexpectedly high in PageRank centrality at a prevalence of 3% of individuals, it provides a possible explanation for why there can be unexpected neurosurgical outcomes when operating in areas of the brain that are traditionally considered as non-eloquent.

### A Common feature associated with L_V6, L_a10p, and L_7PL

One obvious finding for these three parcellations that demonstrated unexpected hubness is that they are on the left cerebral hemisphere, which may be related to the left-sided dominance of most individuals. Secondly, these parcellations all connect to other parts of the brain via the IFOF. L_V6 and L_7PL are both involved in the interpretation of visual input, specifically in the analysis of motion. One would question whether lesioning of these parcellations that have unexpected hubness in certain individuals may confer neurological deficits that are more profound than those described above.

### Cognitive decline after glioma surgery

Cognitive deficits are well-recognized results of glioma resections [5, 23–25]. Many deficits that are of usual concern to the neurosurgeon include those about motor and speech functions. In fact, in some cases, there are no common specific regions that can be used to explain deficits pertaining to neuropsychological facets, such as attention decline, after glioma surgery [23]. Similarly, no regions could be related to working memory capacity in glioma patients [24]. Lastly, surgery in right, otherwise "non-dominant", temporo-parietal junction can result in important deterioration of cognitive control abilities [5]. Our limiting understanding of human brain connectivity in the setting of intracerebral surgeries calls for a better method of understanding brain connectivity in the setting of disease, such as brain tumors. Our current study provides proof-of-concept of a proprietary parcellation method that not only could identify common

important connective hubs but unexpectedly important regions at the individual level as well.

### Replicating previous findings

Our team has previously used diffusion neuroimaging data from the HCP and after applying a parcellation scheme and constructing a weighted adjacency matrix to examine PageRank centrality and areas of eloquence [1]. Importantly, both this study, and the present research, have demonstrated similarities between parcellations that exhibit high PageRank centrality. The present study replicates and expands upon the previous research by using a larger cohort with bilateral graphs and also includes subcortical areas in the analyses. Additionally, the present study uses automated solutions from the Omniscient software which allows for future analysis in an efficient manner.

### Limitations

Several limitations are inherent in the nature of this proof-of-concept study, even though resting-state MRI has been shown to be stable across subjects and is not task-dependent. The cohorts used in this study utilized different scanners and were performed under different settings and different scan times [26, 27]. Although we utilized the same proprietary algorithm on the raw data from the two cohorts, one might expect resultant variants in the ranking of the parcellations. Secondly, this study aimed to defined hubness based on PageRank centrality; the clinical significance of the unexpected hubs as defined by our empiric method is unclear as our primary goal was to investigate whether parcellations that are otherwise considered as low-ranking may have unexpectedly high networking importance.

## Conclusion

In this proof-of-concept study, we demonstrated that lowly-ranked parcellations may represent important hubs in a subset of individuals, highlighting the importance of studying parcellation ranks at the individual level in planning supratentorial neurosurgery. Further studies are needed to characterize the clinical importance and uniqueness of these unexpected hubs.

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**Data availability** The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

### Compliance with ethical standards

**Conflicts of interest** Hugh Taylor, Peter Nicholas, Stephane Doyen and Michael Sughrue are employees of Omniscient Neurotechnologies. No other authors report any conflict of interest.

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