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LABORATORY INVESTIGATION

Beyond eloquence and onto centrality: a new paradigm in planning supratentorial neurosurgery

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Abstract

Purpose Minimizing post-operational neurological deficits as a result of brain surgery has been one of the most pertinent endeavours of neurosurgical research. Studies have utilised fMRIs, EEGs and MEGs in order to delineate and establish eloquent areas, however, these methods have not been utilized by the wider neurosurgical community due to a lack of clinical endpoints. We sought to ascertain if there is a correlation between graph theory metrics and the neurosurgical notion of eloquent brain regions. We also wanted to establish which graph theory based nodal centrality measure performs the best in predicting eloquent areas.

Methods We obtained diffusion neuroimaging data from the Human Connectome Project (HCP) and applied a parcellation scheme to it. This enabled us to construct a weighted adjacency matrix which we then analysed. Our analysis looked at the correlation between PageRank centrality and eloquent areas. We then compared PageRank centrality to eigenvector centrality and degree centrality to see what the best measure of empirical neurosurgical eloquence was.

Results Areas that are considered neurosurgically eloquent tended to be predicted by high PageRank centrality. By using summary scores for the three nodal centrality measures we found that PageRank centrality best correlated to empirical neurosurgical eloquence.

Conclusion The notion of eloquent areas is important to neurosurgery and graph theory provides a mathematical framework to predict these areas. PageRank centrality is able to consistently find areas that we consider eloquent. It is able to do so better than eigenvector and degree central measures.

Keywords Neurosurgery · Neuro-oncology · Graph theory · Eigenvector · Pagerank · Strength · Degree · Centrality · DTI · DSI · Diffusion spectrum imaging

Introduction

One of the most important questions within neurosurgery has always been regarding which areas we ought not transgress and which areas we can cut safely without causing meaningful deficits. It has been known for some time that some areas of the brain are less resilient to transgressions and more readily lead to deficits in function and thus are more essential to observable function of brain. These areas are collectively referred to as the eloquent brain regions [1–4]. There have been attempts to delineate eloquent areas in individual patients by the use of fMRIs, EEGs and similar imaging techniques however, these have not been widely implemented in neurosurgery [5–8].

One promising avenue of research has been the use of graph theory to provide mathematical framework for understanding flow of information in networks such as the brain. Graph theory has been utilised widely to analyse social and biological systems and seems to have potential in analysing the human connectome [9–12]. The use of nodal centrality measures such as degree centrality (DC) and eigenvector centrality (EVC) have been promising [13–15]. However, one criticism of graph theory is the limited understanding of the meaning of these metrics in real neurologic terms [16].

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In this manuscript, we studied the centrality measures in the brain to try to determine what these measures tell us and their utility. PageRank centrality is a graph theory metric similar to DC and EVC but it biases against end nodes or nodes that are simply connected to a single well-connected nodes [13]. A schematic illustrating the differences between these centrality measures is provided in Fig. 1. PageRank was the first algorithm utilised by Google to rank websites by their PageRank centrality [17]. We sought to see if PageRank centrality was a good predictor of areas thought to be eloquent by comparing it to established eloquent areas in the well-known Spetzler-Martin arteriovenous malformations classification system and was also compared to the older centrality measures [18]. Having a mathematical model underpinning eloquence accurately may be the next paradigm shift in our practice of neurosurgery.

Methods

Obtaining connectome data

Neuroimaging data were obtained from the publicly available deidentified, Human Connectome Project (HCP) database (https://humanconnectome.org, release Q3). Diffusion tensor images from eight healthy, randomly selected unrelated subjects aged 22–65, were analysed through fibre tracking analysis (Subjects IDs: 100,307, 105,115, 111,312, 113,619, 115,320, 117,112, 118,730, 118,932). The data was reconstructed using generalized q-sampling in DSI studio [19] (Carnegie Mellon, https://dsi-studio.labsolver.org) with a specified diffusion sampling length ratio of 1.25. The b-values for the diffusion scheme were 990, 1985, and 1980 s/mm^2, trialled in 90 directions using a multi-shell diffusion scheme. The in-plane resolution was 1.25 mm.

Structural matrix generation

To generate a structural matrix, parcellating the cortex into regions of interest (ROI) is necessary. We based these parcellations on the cortical atlas published in 2016 by the HCP under the Glasser scheme that we have extensively studied with 180 identified distinct ROIs [20, 21]. All brain images were registered to the Montreal Neurologic Institute (MNI) coordinate space to standardize comparison between brains. Tractography was performed in DSI Studio [19] (Carnegie Mellon, https://dsi-studio.labsolver.org) using a region of interest approach to initiate fibre tracking from a user-defined seed region [22]. Voxels were automatically traced with a maximum angular threshold of 45 degrees, and tracks with length shorter than 10 mm or longer than 800 mm were discarded. A total of 2.5 million seeds were randomly placed throughout the virtual brain produced by DSI studio to generate said tracts. The cortical atlas with the relevant anatomic ROIs was uploaded into DSI Studio and the number of fibre connections terminating between regions was calculated.

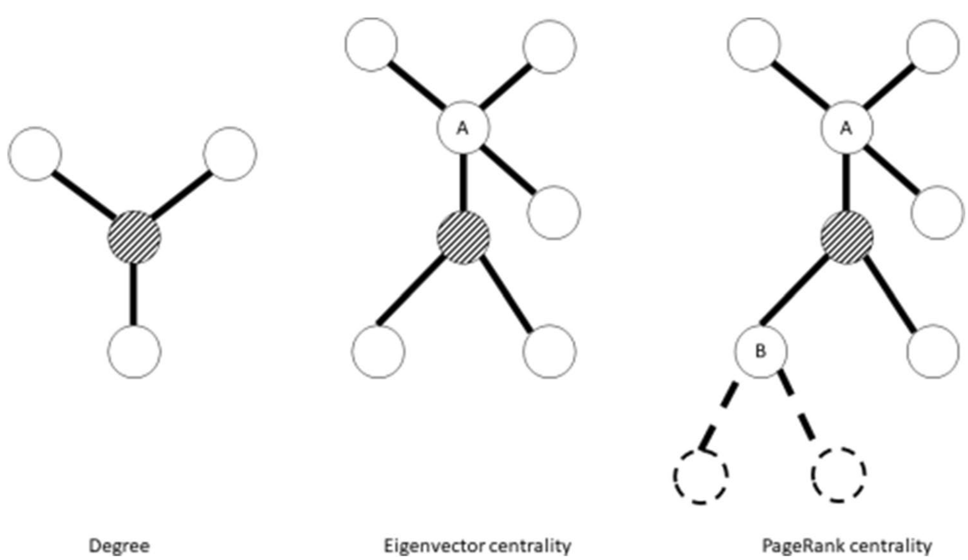

Fig. 1 The degree of the first shaded node is 3; degree is the number of direct connections a node has. The second shaded node to the right has the same degree as the first node but it has a higher eigenvector centrality on the merit of being connected to the high degree node A. PageRank centrality for the third node is penalized due to a single connection to the high degree node A, if two nodes were attached to node B the PageRank centrality measure of the shaded node would go up due to connections to several high degree nodes. PageRank centrality biases against nodes with a single connection to a high degree node whilst eigenvector centrality does not

Computation of graph metrics

Weighted adjacency matrices were generated for each of the brains using DSI studio. These were used to calculate the graph nodal centrality metrics. The weighted matrices were analysed by the Python 3.2 NetworkX module, which contains functions for calculating graph theory metrics [23]. PageRank centrality, EVC and DC were computed for the all 180 ROIs in the Glasser HCP parcellation scheme.

Analysis of graph metric measures

In order to determine if nodal centrality measures were predicting eloquent areas, we ranked the ROIs of the brains in descending order for PageRank centrality, EVC and DC so that a smaller numerical rank indicated a higher nodal centrality. We looked at the top 20 areas for all the brains using PageRank centrality to see how often eloquent areas manifested on the list. We then checked the bottom 20 to see if any of the eloquent areas were in the bottom.

We then looked at the ranks of individual ROIs and calculated the median rank of these ROIs across the three metrics and counted how many eloquent areas appeared in the top 10 for each metric. This was to ascertain how well these graph metrics conveying the notion of hubness adhered to the neurosurgical concept of eloquence.

Statistics and comparison of metrics

To determine which metric was the best predictor of eloquence we compared the metrics. Using literature we identified 35 ROIs that corresponded to the canonical eloquent areas; these included areas 1, 2, 3a, 3b, 4, 6r 8C, 44, TGd, V1, V2, V3, V4, and a24, a24pr, a32pr, AIP, d23ab, v23ab, IP1, IP2, p24, p24pr, p32, p32pr, PBelt, PF, PFm, PGs, PHT, RSC, SFL, STSdp, STSvp, TE1p [2, 3, 5, 24]. These parcellations are highlighted in Fig. 2. The ranks of these 35 areas was noted for each brain for each centrality measure. A summary score of these ranks was calculated by summing the ranks of the 35 important ROIs for each individual. This was done for each of the three graph theory metrics. A lower summary score indicated a closer adherence to the currently established eloquent regions of the brain. The summary scores for the three groups were compared to look for any statistical difference using the Kruskal–Wallis test (with an α of 0.05 with correction for multiple comparisons).

Clinical application

The protocols implemented in the HCP neuroimaging data we used are hard to replicate in clinical practice. So, to address the issue of clinical applicability, we obtained 21 healthy DTI scans from SchizConnect (an opensource collection of publicly available deidentified neuroimaging data) and conducted graph theory analysis on them using the best centrality metric from the previous analysis [25]. The neuroimaging scans available from this database follow common clinical MRI imaging parameters which makes any insights elucidated from their analysis more clinically utilisable.

Results

High centrality areas are often eloquent

We were initially interested to see what cortical areas showed up in the top 20 and bottom 20 ROIs for the brains based on PageRank centrality scores to see if the eloquent 35 ROIs appeared in the lists, as seen in Tables 1 and 2. A description and location of these ROIs is presented under

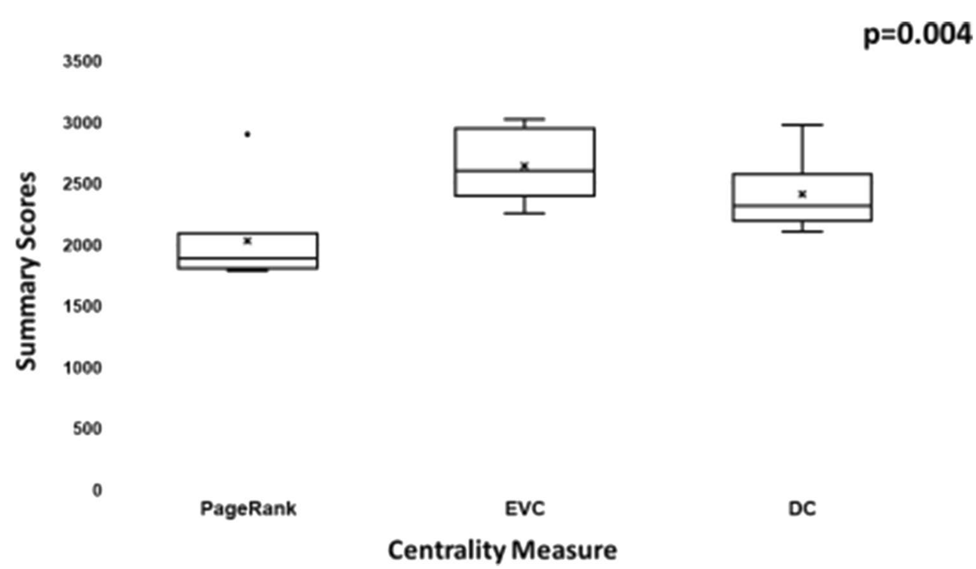

Fig. 2 Comparison of centrality summary scores and Kruskal–Wallis test generated p-value

Table 1 Highest ranked ROIs based on PageRank

Subject 1	Subject 2	Subject 3	Subject 4	Subject 5	Subject 6	Subject 7	Subject 8
V1	PIR	**V1**	PeEc	**V2**	**V1**	PIR	**V1**
V2	**a24pr**	PHA3	FOP3	**V3**	**V2**	**V1**	**V3**
MIP	**V1**	FOP3	**V1**	PHA1	**3b**	**4**	**V2**
8BM	**TGd**	PIR	**TGd**	TGv	**3a**	**V4**	**4**
8C	**V2**	**6r**	PreS	PoI2	**TGd**	MBelt	**6r**
V3	**PFm**	**V2**	FOP4	**3a**	PHA3	AAIC	PoI1
6r	TE2a	FOP2	RI	PEF	TE2a	**6r**	**TGd**
3b	PreS	OP1	**V4**	PI	8Av	**V3**	**2**
TF	**SFL**	**RSC**	H	**4**	**2**	**3a**	PI
4	8BL	**PGs**	**4**	PFop	**RSC**	**V3A**	**STSvp**
TE1p	**6r**	**PFm**	PGi	i6-8	RI	**TGd**	**RSC**
RSC	**V3A**	FOP4	**2**	46	8BL	POS1	**TE1p**
TE2a	**44**	IFSp	V7	45	PeEc	**TE1p**	6ma
IFJp	PH	**V3**	**V3A**	**a32pr**	9p	V3CD	PH
2	**IP2**	**V3A**	**3b**	9p	**4**	PoI2	**V4**
9 m	**RSC**	p10pL	**IP2**	p47r	PreS	PI	**3b**
TGd	**8C**	RI	**RSC**	**V3A**	**V3**	PGi	**6a**
FOP4	STSva	**1**	TF	STSva	**44**	**IP1**	**PFm**
AIP	PGp	PH	**V2**	POS1	**8C**	STGa	46
8BL	**PF**	PHA1	**V3B**	**2**	**1**	H	**IP1**

Eloquent regions are bolded

the Neuroanatomical Supplementary Results section of the Glasser et al.'s paper- A multi-modal parcellation of human cerebral cortex and a more connectomic orientated version is available under the various chapters of Baker et al.'s publication- A Connectomic Atlas of the Human Cerebrum [20, 25–33]. Figure 3 illustrates all the 180 parcellations from

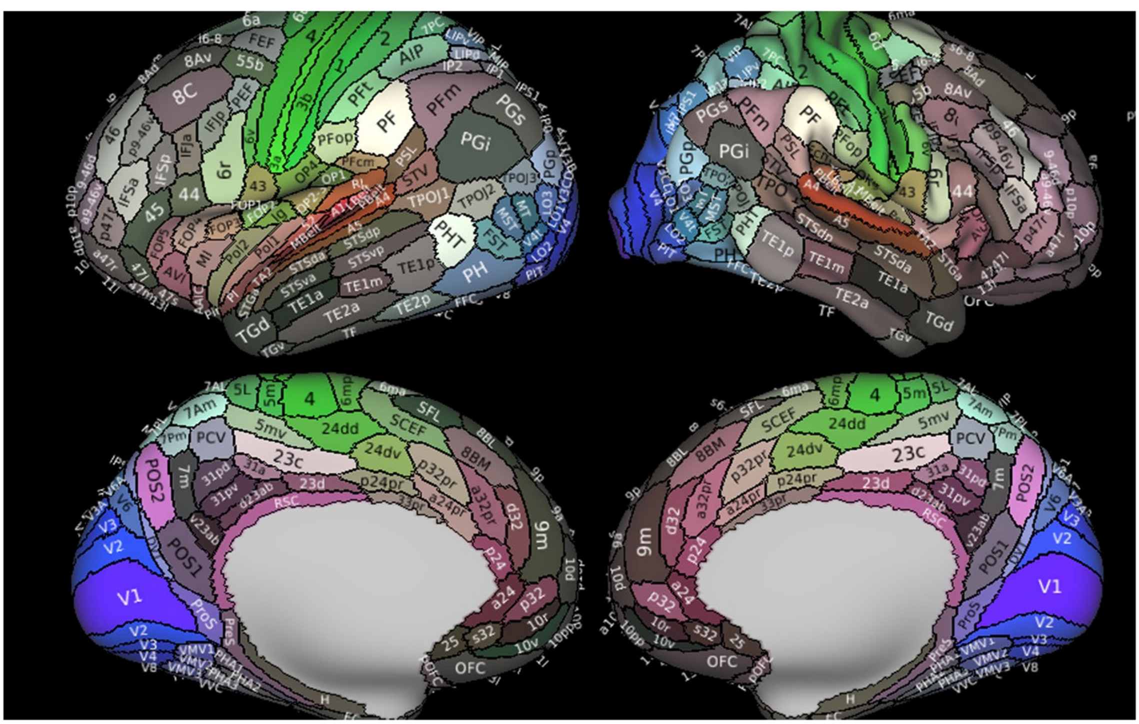

Fig. 3 A lateral and medial sagittal projection of the Glasser Parcellations Scheme

a medial and lateral sagittal view. Top ranks, with lower numbers corresponded to higher nodal centrality scores. We found that areas typically thought of as eloquent made up 88/160 of the ROIs in the top 20 list. Eloquent areas and areas adjacent to them made up 117/160 of the list. This led us to hypothesise that PageRank centrality correlated reasonably well with eloquent brain areas. We then scanned the bottom 20 s to look for any eloquent areas and we found 6/160 that were eloquent as evinced in Table 2.

Nodal centrality measures correspond to eloquence

To look at how well nodal centrality measures correlated with previously known eloquent areas we got the ranks of the all 180 ROIs for the subjects and calculated the median rank of each ROI across the subjects. This was done for all three metrics with lower median ranks corresponding to a high nodal centrality measure. Using PageRank centrality, we found that all of the top 10 median ranked ROIs were eloquent (V1, V2, 6r, TGd, V3, 4, RSC, V3A, 2 and 8C), followed by 6 for EVC (V1,V2, V3, TGd, V3A, V4) and 6 for DC (TGd, V2, V1, V3A, V3, 4) as seen in Table 3 with the bolded areas being eloquent. That said, the other areas that appeared are regarded as areas that are supplementary to the function of the eloquent areas and were either in close proximity of them or had functional connectivity between them for instance, areas like 45 and FOP4. We found the areas that are generally considered to be in the top 10 were

Table 3 Top ROIs based on median ranks for three metrics (PageRank centrality, DC & EVC)

ROIs PR		ROIs DC		ROIs EVC	
V1	1.5	**TGd**	2	**V1**	1.5
V2	4	**V2**	6	**V2**	2
6r	9	**V1**	7.5	**V3**	4
TGd	9	**V3A**	15	**TGd**	7
V3	11	FOP4	16	PreS	10
4	12.5	TF	18	PI	15
RSC	14	**V3**	18	PeEc	15.5
V3A	16	POS2	18.5	**V3A**	15.5
2	17.5	**4**	21	**V4**	15.5
8C	21	45	22.5	ProS	17

Eloquent regions are bolded

thought of as being eloquent also had median ranks that were the lowest when using PageRank centrality followed by DC and with EVC being the least accurate measure.

PageRank centrality is likely to be the best metric to measure eloquence

We compared the nodal centrality measures and how closely they predicted areas thought to be eloquent by calculating the summary scores of the three metrics for the 8 subjects summing the ranks of the 35 conventionally eloquent areas,

Table 2 Lowest ranked ROIs based on PageRank

Subject 1	Subject 2	Subject 3	Subject 4	Subject 5	Subject 6	Subject 7	Subject 8
LO2	25	pOFC	s32	7PL	PIT	TGv	s32
25	PHA2	MT	25	11I	PEF	13I	V6A
pOFC	VMV3	TGv	10v	FEF	LBelt	33pr	10v
52	13I	13I	10r	10v	5 m	5 m	FST
IFJa	pOFC	10v	VMV3	SCEF	MST	MST	13I
s32	VVC	9a	V8	**AIP**	LO2	ProS	AVI
7Pm	7Pm	10 pp	6mp	7Pm	10v	OFC	5 m
5 m	TGv	LO1	47 m	IFJa	**v23ab**	pOFC	PHA2
LO3	VMV1	PIT	VMV1	5 m	13I	TF	52
10v	PHA1	7Pm	TPOJ3	LO2	55b	PeEc	s6-8
FOP2	p47r	s32	**p24**	25	pOFC	7Am	25
OFC	AVI	10d	PHA2	47 s	LO1	7Pm	VMV2
MST	LO3	**p24pr**	5 m	IFJp	7Pm	47 m	DVT
31a	VIP	VIP	OFC	PIT	PCV	PHA1	31pd
VMV1	**a24**	**p24**	PCV	PeEc	s32	EC	pOFC
VVC	PIT	MIP	POS2	5L	TE1m	LIPv	11I
5L	V4t	LO2	13I	p10pL	VIP	5L	TF
PIR	LO1	A1	47I	6v	TPOJ3	VVC	47 m
Ig	OP4	TPOJ3	LO3	STSda	31pv	6ma	10r
TPOJ2	RI	MST	MT	7Am	VMV3	8BL	PCV

Eloquent regions are bolded

Table 4 Summary scores of eloquent ROIs for each subject using the centrality measures

Subjects	Degree centrality	Eigenvector centrality	PageRank centrality
1	2326	2609	1848
2	2103	2348	1814
3	2295	2556	1800
4	2604	3025	2085
5	2979	3025	2902
6	2493	2730	1931
7	2306	2601	2095
8	2165	2253	1785
Median	**2316**	**2605**	**1890**

The median summary scores are bolded

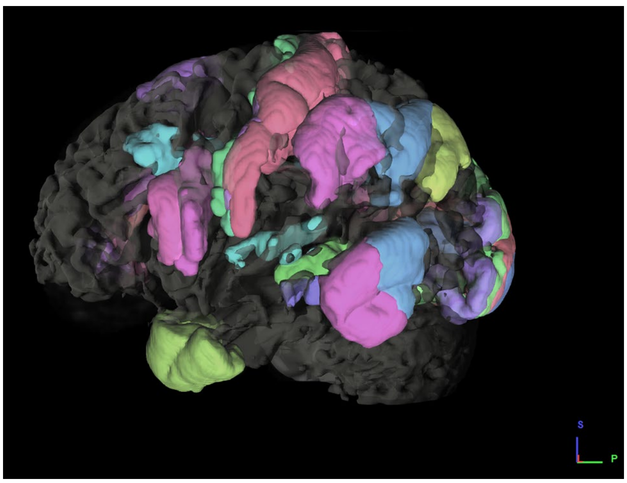

Fig. 4 The 35 parcellation that considered to be canonically eloquent found in the review of the current literature

see Table 4. The median of the summary scores for the PageRank centrality was 1890, followed by DC at 2316 and lastly with EVC at 2605 as seen in Table 4. To establish that there was a significant difference between the three group we conducted a Kruskal–Wallis test on the data that showed that there was with a significance of $p = 0.004$, see Fig. 4. PageRank centrality had the lowest median that signifies a closer adherence to traditional models of eloquence. Upon pairwise comparison, we found a statistical difference between DC and PageRank centrality (p-value being 0.034), between PageRank and EVC ($p = 0.001$) but not between DC and EVC ($p = 0.267$).

We have highlighted the top 10 highly ranked areas for the 8 eight brains using PageRank centrality in Fig. 5a–h. It is clear that there is bit of interpersonal variation with the patients exhibiting a core set of eloquent regions and some of their own unique eloquent regions.

Clinical applicability

We found that using DTI and TI MRI scans that were more in line with clinical protocols also predicted eloquent areas using PageRank centrality as the HCP neuroimaging data. Figure 6 shows the top 10 rated areas that appeared when we looked at the top areas of the 21 brain scans with clinically applicable MRI protocols. Areas 1, 4, 45, SFL (superior frontal lobe parcellation), TE1p (posterior portions of the middle and inferior temporal gyrus) and PFm (a parcellation close to the anterior surface of the angular gyrus) were the ones that were represented at the top of the list. The top 10 areas found using PageRank centrality for the 21 subjects with the clinical neuroimaging data are shown in Fig. 6.

Discussion

It has been known for some time that some parts of the brain are less tolerant to injury than others, these cerebral areas have been termed eloquent brain regions [34, 35]. In this manuscript, we present data that suggest the provocative hypothesis that the areas neurosurgeons have long considered eloquent are highly connected brain hubs. Hubness can be quantified by centrality measures inside of graph theory thus, it may be possible to determine the tolerance of the different regions of the brain to manipulation by quantifying hubs and avoiding them even if their function is not obvious. We may also be able to identify previously unknown hubs and even quantify some aspects of neuroplasticity through our analysis albeit further research is required to achieve these ends.

Hubness and eloquent areas

The concept that brain region eloquence corresponds to mathematical measures of hubness seem plausible to us due to insights from the multidisciplinary study of information flow in networks [36, 37]. There have been studies on fragmentation of network information flow efficiency using a technique called percolation, where nodes are deleted off a graph [38–41]. These studies have shown that in contrast to a more randomly distributed Gaussian networks, the broad-scale degree distributed networks such as the brain, that is, large outliers of nodal centrality characteristics, tend to be more robust to random deletions but more sensitive to deletions of high degree nodes [42–44]. If the nodal deletions are thought of as brain resection then this is consistent with the world's experience doing supratentorial brain surgery [2, 45–48]. Our data strongly suggests that the areas we know typically suffer from surgical transgression in many patients seem to have hub like characteristics in centrality metrics. This supports the idea that neurological deficits

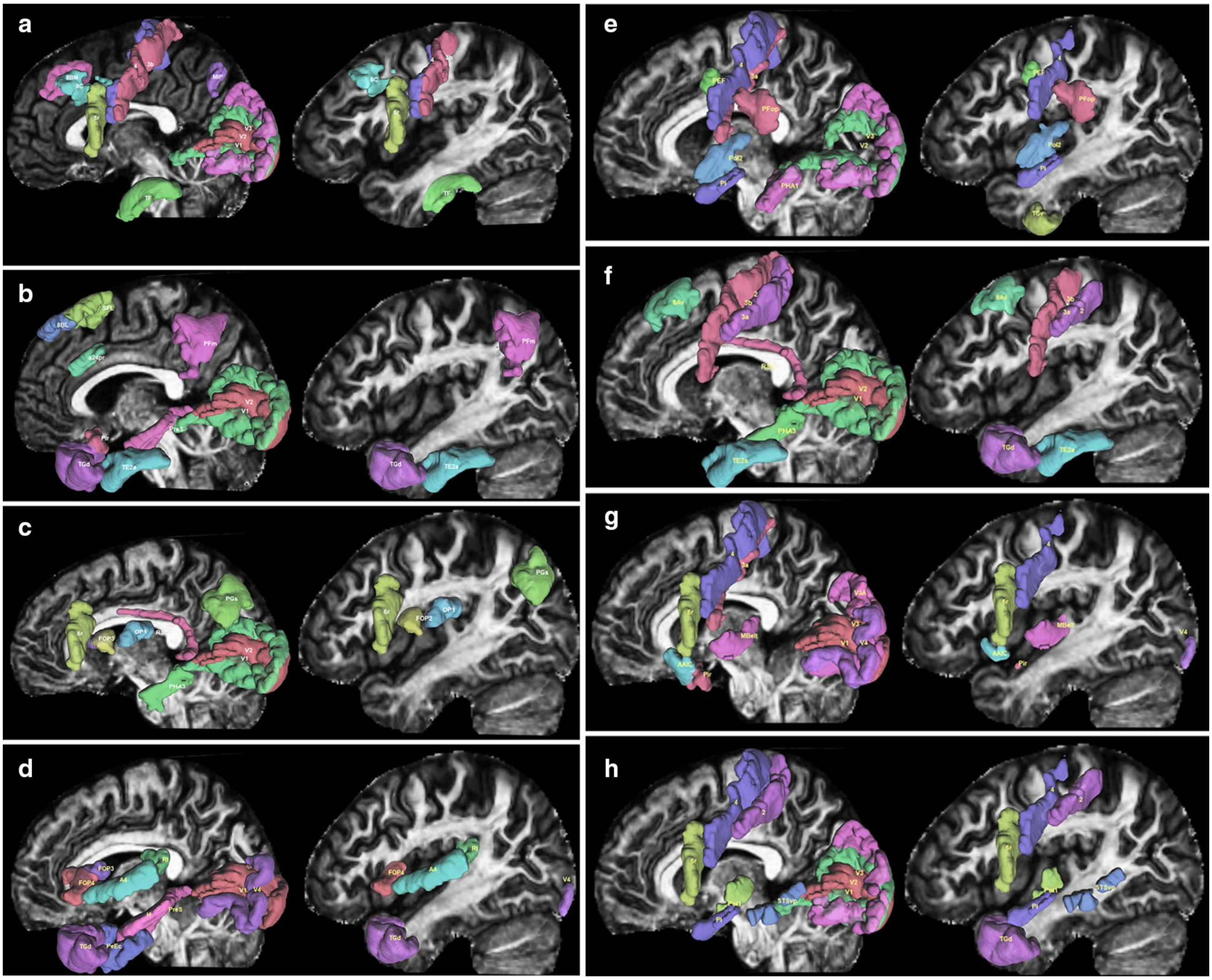

Fig. 5 **a–h** The 10 highly ranked areas for the 8 brains seen from a medial sagittal section and a lateral sagittal section

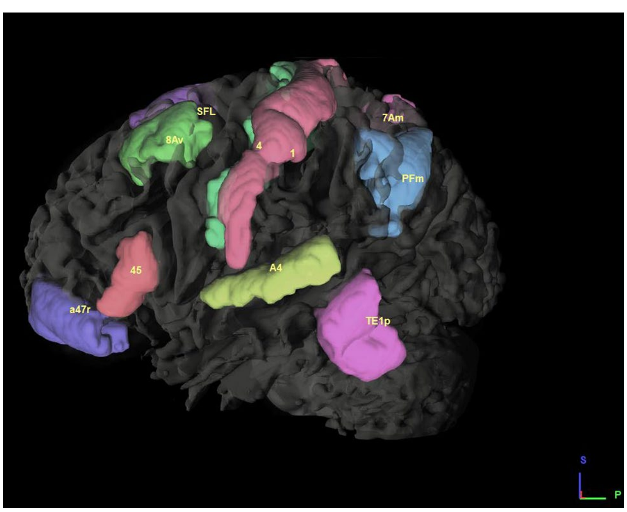

Fig. 6 The 10 highest ranked brain regions using PageRank centrality utilizing the 21 brain scans following common clinical protocols

are predominantly driven by violating hubs and their main connections.

What this means?

This finding raises an important question in neurosurgery; whether we should switch from thinking about how to not transgress eloquent areas to trying to preserve areas of high nodal connectedness. This may help explain why some patients tolerate surgery in areas traditionally considered eloquent better than others due to interpersonal variability in the nodal centrality of the different brains. This presents and interesting line of future study but this requires a study with pathological cases.

This also suggests that some of the cognitive and neurological deficits seen in patients with surgery in supposedly non-eloquent areas might be due to the transgression of a nodal area specific to this patient. Thus, it might be a good idea to avoid transgressing nodal hubs regardless of whether we know their particular functionality. This is a potentially enticing point of future research with individualised surgery plans for patients based on their specific variant of nodal hub characteristics.

PageRank centrality as the best measure of eloquence

Once we realised that high nodal centrality seemed to be measuring eloquence, we sought to see which graph theory metric was best aligned with it. In order to so, we evaluated the three metrics and analysed their ability to highlight areas thought to be eloquent. PageRank centrality which favours highly connected nodes (on both first degree and second-degree connectedness) but biases against end nodes or nodes that are solely connected to one big node, seems to be the best measure of nodal centrality for our data [48, 49].

PageRank centrality adhered closely to our expectations regarding eloquent areas, with most of the eloquent areas appearing in the top 20 s for all 8 subjects. Cortical areas considered eloquent by the Spetzler-Martin arteriovenous malformation scale grading are those associated with sensorimotor, language, visual cortex or regions immediately adjacent to these structures were captured well by PageRank centrality measure. Areas V1 to V4 (primary visual processing areas), 44 (part of the Broca's complex), STSdp (superior temporal sulcus dorso-posterior), TE1P and areas 1, 2, 3a, 3b and 4 (part of the primary motor cortex) featured quite prominently in the top 20 lists for PageRank centrality. There is a clear difference between the three nodal centrality measure using the Kruskal–Wallis test ($p < 0.004$). That said, upon pairwise comparison we concluded that PageRank centrality was better than EVC and DC but no statistically significant difference was found between DC and EVC.

Harnessing these insights into brain surgery and current challenges

Creating a mathematical framework with the help of graph theory metrics will help us back our empirical evidence for eloquent areas of the brain. It may allow us to make predictions about any new non-traditional eloquent areas. It has the potential to be individualised to different brains and might completely replace the previously in place heuristics of where to cut and where to not. What is appealing about graph theory is the relative ease with which we can implement these metrics into software and its applicability to brain scans that use commonly established imaging protocols.

Currently, surgeons identify eloquent areas in the Spetzler-Martin arteriovenous malformation (AVM) classification scheme by relying on anatomical T1 weighted images to help them identify anatomical landmarks that may aid them in doing so [18, 50]. Whilst this works for small lesions, larger lesion have a tendency to distort the morphology of the brains and thus, render the use of anatomical landmarks to identify eloquent regions useless [51, 52]. Since graph theory does not rely on particular anatomical landmarks it may able to improve the surgeons' ability to locate eloquent areas.

Sometimes, larger lesions can change the intrinsic topography of the brain and cause brain reorganisation. This is something graph theory may not be able to overcome currently. Correcting for oedema and being able to parcellate brains affected by pathology further add to this challenge. These issues are being currently tackled by various machine learning models that seek to adjust for the change in topology and morphology caused by brain lesions [5]. This will enable the graph theory analysis to provide insights about brains that have had their topology changed substantially. Our study did not encounter such problems as we used neuroimaging data from healthy adults.

Diffusion spectrum imaging is a technique that has helped generate more accurate tracts and excels in assessing the differences between crossing tracts and is able to adjust well in the presence of a lesion when compared to DTI [53, 54]. This technique is further enhanced by pairing it with newer reconstruction techniques like q-space diffeomorphic reconstruction (QSDR) which has been used to reconstruct diffusion data of patients with chronic stroke that have relatively deviant tractography and connectivity [55]. These newer techniques seem to increase the viability of graph theory's usage in clinical practice after further validation in the future.

The successful prediction of eloquent areas from our PageRank centrality analysis with the 21 brain scans that utilised current clinical protocols suggests that this form of analysis can be integrated to current clinical practice once further studies have validated and replicated our findings. Applying graph theory to a more diverse sample with people with various neurological conditions and brain lesions will help deliver interesting clinical insights. Another exciting avenue of research is the use of the graph theory metric, *global efficiency*. Global efficiency is an expression for how well the brain is connected, it can be thought of as the inverse of the path length connecting different brain regions. It is able to successfully model the changes of the brain network for neurodegenerative conditions and may also help us plan future brain surgery [56–64]. What makes graph theory powerful is that it provides a mathematical model of the brain which permits theoretical considerations and hypotheses about the brain to be studied in a virtual environment and tested against real measures.

So, as it stands, our current use of centrality measures may help us elucidate new eloquent areas, find eloquent areas that may be specific to a particular person and potentially measure neuroplasticity in terms of rigorous mathematical model. Furthermore, due to the nature of the analysis, it can be easily incorporated into the current neurosurgical workflow.

Conclusion

The notion of neurobiological eloquence has dictated how we perform brain surgery. Our data showed how conventional notions of eloquence correlated well with nodal centrality and current notions of hubness. Ultimately, we believe that graph theory analysis of the brains will lead to better personalisation of brain where we are able to minimise post-operative deficits. Graph theory has the potential to deliver clinically relevant endpoint and can be integrated into the current neurosurgical paradigm with ease especially in the milieu of brain mapping software.

Compliance with ethical standards

Conflicts of interest Dr Mike E. Sughrue receives a consulting fee for teaching educational courses for Medtronic and Synaptive. Dr Charles Teo is a consultant for Aesculap. The other authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Ethical approval This study uses publicly available deidentified MRI data from the Human Connectome Project (HCP) and thus does not require an ethics approval.

Informed consent The data this study utilises comes from the HCP which obtained informed consent from the participants.

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