Topological Characteristics Associated with Intraoperative Stimulation Related Epilepsy of Glioma Patients: A DTI Network Study

Jianing Yang  
Beijing Tiantan Hospital

Chunyao Zhou  
Beijing Tiantan Hospital

Yuchao Liang  
Beijing Tiantan Hospital

Yinyan Wang  
Beijing Tiantan Hospital

Lei Wang (✉ wanglei_tiantan@163.com)  
Beijing Tiantan Hospital  https://orcid.org/0000-0002-6916-704X

Research Article

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Abstract

**Purpose** Awake craniotomy with intraoperative stimulation has been utilized in glioma surgical resection to preserve life quality. While 5-20% of cases may occur epilepsy during the procedure which leads to severe consequences. The study aimed to discussing the mechanism of intraoperative stimulation-related epilepsy (ISE) with DTI based graph theoretical analysis.

**Methods** 20 patients with motor-area glioma were enrolled and divided into 2 groups (Ep and nEp) according to whether there was ISE. Additionally, a group of 10 healthy participants matched by age, gender and education year were also involved. All participants underwent T1, T2 and DTI. Graph theoretical analysis was applied to reveal topological characteristics of the white matter networks.

**Results** Three connections were found to be significantly lower in at least one weighting in Ep group. They are the connection between A1/2/3truL and A4ullL, A1/2/3truR and A4tR, and A6mL and A6mR. Global efficiency was found to be significantly decreased while the shortest path length increased in Ep group in at least one weighting. Ten nodes exhibited significant difference in the nodal efficiency and degree centrality analysis. The nodes A6mL and A6mR showed markable decrease in total four weightings in Ep group.

**Conclusion** The hub nodes A6mL and A6mR, get disconnected in the patients with ISE, causing subsequent lower efficiency of global and regional network. The findings provide basis for presurgical assessment of ISE, for that caution should be taken when it involves hub nodes during intraoperative electrical stimulation.

Introduction

Glioma is the most common original neoplasm in central nervous system, whose standard treatments include surgical resection and following chemo-radiotherapy[1, 2]. Awake craniotomy (AC) with intraoperative electrical stimulation has been used for the identification of sensorimotor cortex and other functional regions with high efficiency and accuracy, which is considered to preserve the quality of life to the utmost[3-5]. However, 5-20% of cases may occur seizure during this procedure, interfering patients’ complying as well as causing poor outcomes[6, 7]. Though treatments like propofol sedation and cold ringer’s lactate may seize the seizure onset, the happening of intraoperative stimulation related epilepsy (ISE) could still lead to serious postoperative complications, such as motor deficits or cognitive impairment[6, 8]. It is currently acknowledged that preoperative epilepsy, tumor location, repeated stimulation, and high stimulation current are predisposing factors of ISE[9]. However, the mechanisms of ISEs are still rarely studied, currently. ISE seems random and unpredictable, hence becomes one of the main risks of AC. Therefore, the prediction and prevention of ISE needs to be investigated.

The mechanism of epilepsy, though generally researched, remains partially unclear. It is already known that the brain networks are complicated both in its anatomical substance and physiological functions[10], meanwhile, most subtypes of epilepsy works in a network pattern[11-13]. Most general
seizures are related to sensorimotor cortex discharge, and will further impair functional or structural connections in several networks. Therefore, the graph theory, focusing on topological connectivity patterns, can be utilized to analyze the structural alterations in brain networks of epilepsy patients. However, the association between ISE and alterations in subcortical networks as well as their topological attributes remains unknown.

Diffusion tensor imaging is an advanced technique to quantitively measure subcortical structure non-invasively[14][15], which, can be the tool of revealing white matter structure changes under the conditions of multiple brain functional or structural disorders. The abnormality of DTI networks can represent the dysfunction of brain networks in epilepsy patients. Therefore, diffusion metrics as well as graph theoretical attributes could provide details on characteristics of epilepsy[10, 16, 17], normally reflected as global efficiency decreased and the shortest path length increased in patients with epilepsy[18, 19]. Further, some topological attributes including small-world are considered to have synchrony effect in epilepsy development, by stronger clustering co-efficiency and shorter path length[20]. Therefore, identifying the characteristics of subcortical networks in patients with ISE will help to better understand the mechanism of seizure onset, and further increase the prognostics of suspectable patients.

This study, with DTI technique and graph theory, aims at identifying the characteristics of ISE in network connection prospect, in order to further help reducing ISE occurrence.

**Methods**

The study protocol was approved by the institutional review board of our hospital. All participants provided written informed consent before data acquisition.

**Participants**

A total of 20 patients with frontal glioma in our hospital were retrospectively recruited. All patients were included following the criteria as: (a) older than 18 years; (b) pathologically diagnosed as WHO II-IV glioma according to the WHO (2016) standard for CNS neoplasm; (c) more than nine years of school education; (d) no history of presurgical biopsy, radiotherapy or chemotherapy. The exclusion criteria were: (a) contraindications for MRI; (b) head motion greater than 1 mm in translation or 3° in rotation; (c) history of AED usage before MRI acquisition. Finally, 20 patients (10 males) were enrolled in the study. Additionally, a group of 10 healthy participants matched by age, gender and education year were also involved.

**MRI acquisition**

All MRI data were acquired through a MAGNETOM Prisma 3T MR scanner (Siemens, Erlangen, Germany). Anatomic images were collected with T1 magnetization-prepared rapid acquisition of gradient echo
(TR=2300 ms, TE=2.3 ms, flip angle=8°, Field of View, FOV=240*240 mm, voxel size=1.0×1.0×1.0 mm
3,
slice number=192). T2-FLAIR sequences were used to acquire the tumor mask (TR = 3200 ms; TE = 87 ms; 
FA = 150°; FOV = 220 mm × 220 mm; voxel size = 0.9 mm × 0.9 mm × 5 mm; slice number = 25). DTI data 
were acquired using single shot, echo planar imaging sequence (TR=6000 ms, TE=103 ms, axial 
slices=75, resolution=2.0*2.0*2.0 mm, flip angle = 75°; FOV = 230 mm × 230 mm; voxel size =2.0 mm 
×2.0 mm ×2.0 mm, number of directions=30, b=0/1000 s/mm
2, EPI factor=154).

The DTI data preprocessing

Preprocessing and analysis of diffusion metrics was performed with PANDA toolbox. The detailed 
preprocessing, tractography and network construction steps have been clarified by Cui et al [21]. Briefly, 
after converting raw DICOM data to a Nifti format, PANDA implemented steps to extract basic DTI 
metrics, including brain mask extraction, eddy current effect correction, averaging multiple acquisitions, 
diffusion tensor calculation, and metrics production. Atlas based FACT deterministic fiber tracking was 
implemented with the pre-set motor-sensory network: (angle threshold= 45°; FA threshold=0.2).

Stimulation protocol

The functional cortex was identified with an Ojemann stimulation system, 5mm diameter (intensity, 1–6 
mA; frequency, 60 Hz; square wave). The stimulation current began at 1 mA, and was increased by 0.5 
mA until the patient showed unconscious limbal movements (precentral gyrus) or transient numbness 
(postcentral gyrus), thus, to establish the stimulation threshold. Once the stimulation threshold was 
established, the stimulation current would be unchanged and used to identify the eloquent cortex and 
subcortical structures. The stimuli duration for identification was 1 second for motor- and sensory-related 
cortex and 4 seconds for language-related cortex. No site was continuously stimulated. The iced Ringer’s 
solution would be used in case of ISE occurrence. If the epilepsy lasts over 10 seconds, benzodiazepine 
was administered, and the operation had to be temporarily ceased. ECoG was not utilized during this 
 procession.

Tumor Region of Interest extraction

The regions of glioma were manually segmented by two experienced neurosurgeons independently. For 
low-grade gliomas, ROIs were extracted based on T2-FLAIR, while for anaplastic glioma and 
glioblastoma, ROIs were extracted based T1-contrast enhancement. If the masked tumor region varied 
over 5% between the two surgeons, a neuro-radiologist with 20-year-experience would make the final 
decision. All tumor masks were then normalized into the MNI standard space using the clinical toolbox 
package in SPM8 (http://www.fil.ion.ucl.ac.uk/spm/software/spm8/) (Supplementary Figure 1b). Finally, 
all normalized tumor masks were overlapped to create tumor volume overlapping image (Supplementary 
Figure 2).
Network Construction

The nodes considering the motor-sensory network were extracted from an open access brain atlas, “brainnetome atlas” (http://www.brainnetome.org/). To avoid neurovascular uncoupling or a tumor occupying effect, the regions invaded by gliomas were excluded. To construct white matter (WM) connectome matrix, deterministic fiber tracking was used to track WM connections for all possible pairs of nodes. Consequently, for each subject, a 22*22 white matter connectome matrix was therefore constructed, each edge in the matrix were weighted by averaged Fiber Number (FN), Fractional Anisotropy (FA) and Matrix length (FL).

Graph theoretical measures

Before each individual matrix is delivered into graph theoretical analysis, a backbone method with a threshold above 75% was applied to minimize error connections caused by normalization error or partial volume effect. Global and nodal topological properties, including the global efficiency, local efficiency, nodal efficiency, degree centrality, and small-world properties (gamma, lambda, and sigma) were calculated by GRETNA toolbox[22] for each patient and healthy control (Supplementary material). Binary, FA, FN and FL weighted networks were used in the calculation of each topological property.

Statistical analysis

Clinical characteristics were compared between ISE group, non-ISE group and controls utilizing one-way ANOVA in R (https://www.r-project.org/). One-way ANOVA and with False Discovery Rate correction and post-hoc test was used to calculate the differences of inter-group WM connections and nodal properties.

Results

Demographic characteristics

A total of 20 patients (9 males) with frontal-lobe glioma and 10 healthy controls (5 males) were enrolled in this study. The patients were divided into 2 groups according to whether there was epilepsy onset induced by intraoperative stimulation. On this case, the three groups are: glioma patients with intraoperative stimulation-induced-epilepsy (Ep, n = 10), glioma patients without intraoperative stimulation-induced-epilepsy (nEp, n = 10), control group (con, n = 10). (Supplementary Table 1) No intergroup significant differences were observed in gender, histology, IDH status, education level, tumor volume and stimulation current during surgery (P > 0.05, one-way ANOVA).

Connections differences
Except for six nodes that was invaded by tumor, all the connections in motor-sensory networks were compared among the Ep group, nEp group and control group with binary and weighted (FA, FL and FN) networks. Among them, three connections showed significant intergroup differences. They are the connection between left medial area 6 (A6mL) and right medial area 6 (A6mR) in bilateral superior frontal gyrus, left area 4 (A4uL) representing left upper limb region in right precentral gyrus and left area 1/2/3 (A1/2/3truL) representing left trunk region in right postcentral gyrus, and right area 4 (A4tR) representing right trunk region in left precentral gyrus and right area 1/2/3 (A1/2/3truR) representing right trunk region in left postcentral gyrus, respectively. (Supplementary Table 2) Relative to the control group, Ep group showed lower FA and FN (FA, \(P = 0.017\); FN, \(P = 0.0014\)) in the A1/2/3truL and A4uL connection. Besides, the FN was also significantly lower in nEp group compared to control in this connection (\(P = 0.0017\)). As for the connection between A1/2/3truR and A4tR, FN in control was significantly higher than both in Ep and nEp group (\(P = 0.0008\), \(P = 0.0018\), respectively). FL also decreased in Ep and nEp group than in control (\(P = 0.0017\), \(P = 0.0014\), respectively). Another connection to be found different is between A6mL and A6mR, in which the Ep group exhibited lower FA than both control and nEp group (\(P = 0.0012\), \(P = 0.0028\), respectively), but no significant differences in FA between nEp group and control. (Figure 1)

Global properties differences

Global efficiency, small-world properties, hierarchy, synchronization, and rich club were selected to measure inter-group global differences with one-way ANOVA. (Table 1) Global efficiency and shortest path length showed significant differences in binary and all three weighted networks (\(P < 0.01\), \(P < 0.01\), respectively). The significant global attributes were further analyzed by post-hoc. The global efficiency in Ep group markedly decreased than control in binary, FA, FN, and FL (\(P < 0.01\) in binary, FA, FN, and \(P = 0.0012\) in FL, Figure 2a). The difference between control and nEp group is also significant in the above four weightings (\(P = 0.153\) in binary, \(P = 0.0041\) in FA, \(P < 0.001\) in FN, and \(P = 0.0072\) in FL, Figure 2a). Compared to nEp group, Ep group only showed lower global efficiency in FA weighting (\(P = 0.031\), Figure 2a). Considering shortest path lengths, Ep group showed noticeable increasing of shortest path length than the control group in the above four weightings (post-hoc, \(P = 0.0032\) in binary, \(P = 0.0011\) in FA, \(P = 0.0070\) in FN, and \(P = 0.0032\) in FL, Figure 2b). Likewise, the shortest path length of nEp group is also significantly higher than control (post-hoc, \(P < 0.0203\) in binary, \(P = 0.0055\) in FA, \(P < 0.001\) in FN, and \(P = 0.0160\) in FL, Figure 2b). Compared to the nEp group, Ep group only shows markedly increase of shortest path length in FA weighting (post-hoc, \(P = 0.0363\), Figure 2b).

Nodal properties differences

The nodal properties which presenting local efficiency related to the motor-sensory network were all measured, including nodal efficiency, betweenness centrality, degree centrality, nodal shortest path length and clustering coefficient. Among them, the nodal efficiency and degree centrality were found to have inter-group significant differences. (Supplementary Table 3) On nodal efficiency, a total of ten nodes
exhibited significant difference (A6mL, A6mR, A4tR, A4ulL, A4ulR, A4ullL, A123truL, A123truR, A123ulhfL, and A4hfL) in at least one weighting. Among them, A6mL and A6mR showed markable difference in all four weightings (Figure 3). (Supplementary Table 4) As for degree centrality, the analytic results seemed similar to the nodal efficiency, with seven nodes illustrating significant difference (A6mL, A6mR, A4tR, A4ulL, A4ulR, A123truL, and A123truR), and A6mL and A6mR also showed markable difference in total four weightings from among. In addition, A6mL and A6mR also exhibited inter-group disparity in betweenness centrality. (Figure 4)

We further analyzed the nodal efficiency and degree centrality of A6mL and A6mR by subsequently post-hoc test in four weightings. (Supplementary Table 5) Compared to the control, Ep group showed markable decrease of nodal efficiency in all four weightings of both A6mL and A6mR \( (P = 0.003, 0.002 \) in binary, \( P = 0.002, 0.001 \) in FA, \( P = 0.004, 0.004 \) in FN, and \( P = 0.004, 0.003 \) in FL, respectively). Significant difference was also obtained between Ep and nEp group in binary, FA, and FL weightings of both A6mL and A6mR \( (P = 0.004, 0.007 \) in binary, \( P = 0.004, 0.005 \) in FA, and \( P = 0.0016, 0.023 \) in FL, respectively). As for the comparison between nEp and control, only FN showed decrease in both A6mL and A6mR \( (P = 0.011, 0.009, \) respectively). (Supplementary Table 6) The results of degree centrality analyzed by post-hoc test among the three groups are very close to the nodal efficiency mentioned above, showing the significant difference \( (P < 0.05) \) between Ep and control of both A6mL and A6mR, and the rest are similar too. Furthermore, when comparing the degree centrality among nodes, A6mL and A6mR had highest degree centrality value in FN and FL networks, and relatively high degree centrality value in binary and FA networks (Supplementary Figure 3).

**Discussion**

All 20 subjects were divided into two groups (Ep and nEp) according to the occurrence of ISE. The comparison of connections in motor-sensory networks among three groups showed partial derangement in ISE patients. The following analysis of global topological properties exhibited remarkable alternations in ISE patients, with worse network efficiency and longer shortest path length. Considering the robust results on global topology, nodal properties were further measured, among which A6mL and A6mR exhibited markable decrease in nodal efficiency and degree centrality in Ep group.

The current study involved patients with left-sided motor-area glioma, with or without ISE. We only took 28 subregions of motor-sensory network into consideration (the brainnetome 246 atlas). Since 1) ISE always occurs around the stimulation point, which is normally located at or near the motor cortex (or SMA), and 2) the motor-sensory network is more vulnerable in major epileptic seizure. Further, controlling the tumor related mass-effect is a major challenge of network analysis in glioma patients. Tumor’s oppression, invasion or infiltration will alter its surrounding anatomical structure, causing inaccuracy in the normalization procedure. As a result, it will cause mistakes in region of interests locating and atlas-based fiber tracking. Under such concern, we made a tumor-overlapping map, and all subregions within the map were avoided. Thus, a total of 22 subregions were finally included in the analysis.
Our results demonstrated several subcortical connections that showed tendency of degeneration in FA, FN and FL. Among them, two connections (A6mL to A6mR, and A4ulL to A123truL), both showed decreased FA in Ep group comparing to nEp and healthy control. FA is thought to be the most sensitive parameter on measuring white matter connectome abnormalities in SMA originated epilepsy, as decreased-FA equaling decreased orientation and fiber density[23]. In the current study, it also posed that the main difference between Ep group and other two groups is the FA weighted connections, especially between A6mL and A6mR. The very connection between interhemispheric SMA have been proved to be reduced in glioma patients[24], indicating that this connection is vulnerable in the procedure of tumor occurrence, and the impairment of the white matter connection might be related to epilepsy occurrence[23].

Brain network dysfunction is known to be associated with the onset of epilepsy[12, 25, 26]. In the current study, all individual networks exhibited small-world characteristic, indicating that though partially involved by tumor or tumor-related edema, the entire network of these patients still exert better efficiency with long distance connections[20, 27]. The rise of global shortest path length is always associated with the decrease of global efficiency, indicating the disruption of brain network in ISE patients[28, 29]. The very network damage is proved to be continent and dynamic, further again increases the network disruption and finally lead to vicious spiral[12, 30]. The above results, together with the very topological features of several decreased connections demonstrated that both local segregation and global disruption in the ISE patients, which is in line with prior network studies[19]. The white-matter connections that mentioned above may be one of the causes of collapsed networks[19]. Eddin et al.[31] also assessed the network efficiency of pediatric epilepsy and turned out to be significantly lower. The authors analyzed partial functional network of those kids, discovering that patients tended to activate the whole brain network while the healthy controls only made use of a smaller independent network, to achieve the same task[31]. Hence, the lower efficient network may perform worse in information transferring therefrom need to trigger a larger subnetwork, suggesting less precision and more randomness. When there are white matter degeneration or reorganization, the consequently reducing connectivity will finally lead to the consensus network efficiency alteration. Moreover, the network exhibited more randomness and ipsilateral hub reorganization in epilepsy patients[31], suggesting more synchronization and less precision of aberrant network. It can be deduced that the less efficient network will cause larger and random activation, subsequently inducing hyperexcitability and vulnerability to external stimulation, which reflects as easy collapse during intraoperative stimulation[32, 33].

Epilepsy is also known to cause regional network disruption[34]. Further nodal analysis brought out the significant decrease of nodal efficiency and degree centrality of A6mL and A6mR in Ep group, together with other nodes surrounding them. Previous findings of structural connectivity of supplementary motor area (SMA) have exhibited the preservation of connectivity in frontal lobe epilepsy patients, giving evidence to the strength and stability within connections in SMA[23]. Interestingly, all participants showed relatively higher degree centrality at A6mL and A6mR than other nodes (Supplementary Figure 3), representing their importance as “hub nodes” in the motor sensory network. Moreover, variable differences of hub nodes have been investigated in several epilepsy-related findings, demonstrating the
centralization or decentralization of some nodes that play an important role in the etiology of epilepsy[35, 36]. In our study, ISE patients showed decrease of degree centrality value in bilateral SMA. This can be accounted that epilepsy location usually source from isolated cortex around tumor mass, due to the subcortical impairment[37-39]. Therefore, the decreased degree centrality might be caused by reduced connectivity of isolated cortex[36]. It is supposed that the impaired connectivity with other areas and the diminished degree centrality will again induce isolation at nodal level[37, 40]. On this prospective, the decreasing of nodal efficiency may also generate from the impaired inter-regional connection and attribute to the isolation of nodes. Moreover, the connection between A6mL and A6mR, as interhemispheric connection, also showed lower FA in the ISE patients, which re-affirm their isolation. Consequently, it is the preserving connectivity inside nodes and external isolation that disables hub nodes from interacting with the whole network, finally leads to the segregation and distribution of network hubs. Therefore, it should be cautious when the nodes A6mL and A6mR are involved during intraoperative stimulation since their critical role in ISE.

Conclusions

The SMA (A6mL and A6mR), which are likely to be the hubs of motor-sensory network, get disconnected in the patients with ISE. The subsequent lower efficiency of global and regional network might be brought about from the hub nodes isolation. This finding provided basis for presurgical radiological assessment, for that caution should be taken when it involves the nodes A6mL and A6mR during electrical stimulation.

Declarations

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Tables

Table 1 Global properties with significant inter-group differences

| Global properties              | weighting | \( P \) (ANOVA) | Post-hoc \( P \) value |
|-------------------------------|-----------|-----------------|------------------------|
|                               |           | Ep vs. Con      | nEp vs. Con | Ep vs. nEp |
| Global efficiency             | Binary    | 0.0014          | <0.001       | 0.0153     | 0.1054     |
|                               | FA        | <0.001          | <0.001       | 0.0041     | 0.031      |
|                               | FN        | <0.001          | <0.001       | <0.001     | 0.5301     |
|                               | FL        | 0.0018          | 0.0012       | 0.0072     | 0.1655     |
| Shortest path length          | Binary    | 0.0032          | 0.0032       | 0.0203     | 0.1102     |
|                               | FA        | <0.001          | 0.0011       | 0.0055     | 0.0363     |
|                               | FN        | 0.0056          | 0.0070       | <0.001     | 0.2452     |
|                               | FL        | 0.0031          | 0.0032       | 0.0160     | 0.0733     |

Figures
Figure 1

Connections differences in the A1/2/3truL and A4ulL connection, Ep group showed lower FA and FN. The nEp group also showed lower FN than control in this connection. In the A1/2/3truR and A4tR connection, FN in control was significantly higher. FL in control was also significantly higher than Ep and nEp groups. In the A6mL and A6mR connection, the Ep group exhibited lower FA than both control and nEp group, but no significant differences between nEp group and control.
Figure 2

Global properties differences (a) The global efficiency of Ep group markedly decreased than control in binary, FA, FN, and FL. The global efficiency of nEp group is also significantly decreased than control in the above four weightings. Ep group only showed lower global efficiency in FA weighting comparing to nEp. (b) The shortest path lengths of Ep group showed noticeable increase than the control group in the above four weightings. Likewise, the shortest path length of nEp group is also significantly higher than control. Ep group only showed increase of shortest path length in FA weighting comparing to the nEp.
Figure 3

Nodal efficiency of A6mL and A6mR in all four weightings. Nodal efficiency of A6mL and A6mR both showed significant difference in Ep group than the other two groups in all four weightings.
Figure 4

Nodal properties differences (a) Ten nodes exhibited significant difference in at least one weighting of nodal efficiency. A6mL and A6mR exhibited significant difference in all four weightings of nodal efficiency. (b) Seven nodes exhibited significant difference in at least one weighting of degree centrality. A6mL and A6mR exhibited significant difference in all four weightings of degree centrality. (c) A6mL and A6mR also exhibited inter-group disparity in betweenness centrality.

Supplementary Files

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