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RESEARCH

A longitudinal multimodal MRI study of the visual network in postoperative delirium

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Abstract

Although structural and functional damage to the brain is considered to be an important neurobiological mechanism of postoperative delirium (POD), alterations in the visual cortical network related to this vulnerability have not yet been determined. In this study, we investigated the impact of alterations in the visual network (VN), as measured by structural and functional magnetic resonance imaging (MRI), on the development of POD. Thirty-six adult patients with frontal glioma who underwent elective craniotomy were recruited. The primary outcome was POD 1–7 days after surgery, as assessed by the Confusion Assessment Method. Cognition before surgery was measured by a battery of neuropsychological tests. Then, we evaluated preoperative and postoperative gray matter volume (GMV) and functional connectivity (FC) alterations by voxel-based morphometry and resting-state functional MRI (rs-fMRI) between the POD and non-POD groups. Multiple logistic regression models were used to investigate the associations between neuroimaging biomarkers and the occurrence of POD. Compared to those in the non-POD group, a decreased GMV in the fusiform gyrus (0.181 [0.018] vs. 0.207 [0.022], FDR$p = 0.001$) and decreased FC between the fusiform gyrus and VN (0.351 [0.153] vs. 0.610 [0.197], GFR$p < 0.001$) were observed preoperatively in the POD group, and increased FC between the fusiform gyrus and ventral attentional network (0.538 [0.180] vs. 0.452 [0.184], GFR$p = < 0.001$) was observed postoperatively in the POD group. According to our multiple logistic regression analysis, age (Odds ratio [OR]: 1.141 [1.015 to 1.282], $P = 0.03$) and preoperative fusiform-VN FC (OR 0.001 [0.001 to 0.067], $P = 0.01$) were significantly related to risk of POD. Our findings suggested that preoperative functional disconnectivity between fusiform and VN might be highly involved in the development of POD. These findings may allow for the discovery of additional underlying mechanisms.

Keywords Postoperative delirium · Visual network · Multimodal MRI · Frontal glioma

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Introduction

Delirium is an acute neuropsychiatric syndrome characterized by acute and fluctuating changes in cognition, inattention, and an altered level of consciousness. Postoperative delirium (POD) is one of the most common postoperative complications in surgical patients and is associated with poor short-term and long-term outcomes, including hospital morbidity, increased risk of institutionalization, mortality, and long-term cognitive dysfunction (Huang et al., 2021; Jin et al., 2020; Peden et al., 2021; Swarbrick and Partridge, 2022). Therefore, POD has become a significant global health challenge that needs urgent attention (O'Regan et al., 2013). Unfortunately, there are currently limited effective therapies for delirium, largely because of the inadequately understood pathogenesis of this condition.

In recent years, neuroimaging has become an important research technique for exploring the neuronal pathogenesis of POD (Peden et al., 2021). Neuroimaging studies on POD have revealed that structural impairment as well as structural and functional disconnectivity in cognitive-related brain regions and/or networks may be important neurobiological mechanisms involved in the development of POD, and multimodal functional networks, including the salience network (SN), default mode network (DMN) and central executive network (CEN), may play integrative roles in the development of POD (Casey et al., 2020; Cavallari et al., 2016; Ditzel et al., 2023; Fislage et al., 2023; Katsumi et al., 2022; Oh et al., 2019; White et al., 2021; Winterer et al., 2021; Young, 2017). So far, several researches suggest that vision impairment is closely associated with cognitive functioning, probably because vision impairment may induce the structural and functional alteration in the brain (Nagarajan et al., 2022; Zheng et al., 2018). Furthermore, the recent researches and meta-analysis also indicate that visual impairment significantly increased the risk of delirium (Li et al., 2023a, 2023b; Morandi et al., 2021; Sileshy et al., 2022; Zheng et al., 2018). Inouye and colleagues underlined the importance of the patients for the presence of visual impairment, providing them with glasses if needed (Inouye et al., 1999). This approach has been proven to be effective for delirium prevention (Inouye et al., 1999). Additionally, light therapy seems to be a promising strategy for preventing and treating POD (Chong et al., 2013; Zou et al., 2022). However, the mechanism underlying the association between vision impairment and delirium have not yet been fully characterized. Fislage et al. suggested that structural and functional abnormalities of the thalamus were associated with the risk of developing POD (Fislage et al., 2023). The thalamus is an important relay in underlying pathways that actively shapes the processing of various sensory signals before the information reaches the cerebral cortex (Brinkmann et al., 2021). These findings indicate that dysfunctions in sensory and perceptual processing could serve as the neural basis for common symptoms of POD, such as agitation, inattention and hallucinations. Therefore, we hypothesize that the visual network (VN4), which serves as the most crucial "source" for communication between the brain and the outside world, may play an important role in the development of POD (Haupt and Huber 2008). To date, the VN has been reported to play a regulatory role in neuropsychiatric disorders; for example, several studies have shown that abnormalities in the visual cortex have been detected in patients with major depressive disorder, and the mechanisms of action of several antidepressants coincide with improvements in the structure and function of the visual cortex (Wu et al.,). Meanwhile, depression is an important predictor of POD (Falk et al., 2021; Zhang et al., 2020). However, few studies have investigated the effect of the VN on the development of POD.

Because the brains of neurosurgical patients are extremely vulnerable and these patients are prone to delirium, POD in this population has received growing attention in recent years (Huang et al., 2022; Kappen et al., 2022; Li et al., 2023a, 2023b). Our previous research revealed that patients with frontal lobe gliomas are at especially high risk for POD among neurosurgical patients, with an incidence rate as high as 37.3% (Huang et al., 2022). To further explore the neural mechanisms of POD in this patient population, we carried out a prospective study and longitudinally collected multimodal neuroimaging data and cognitive data from patients with frontal lobe gliomas. In the present study, we conducted a second analysis of the longitudinal neuroimaging data of this cohort focusing on the VN to further investigate the impact of the VN on the development of POD. We hypothesize that preexisting VN deficits may constitute an important factor in the neural pathological basis of POD, and these deficits will be exposed and aggravated when patients are experiencing perioperative stress, thus playing an important role in the development of POD in our subjects.

Materials and methods

Participants

A prospective cohort of adult patients with frontal glioma was obtained from the neurosurgical department of Beijing Tiantan Hospital, Capital Medical University, Beijing, China, from May 2022 to September 2022. The study was registered at ClinicalTrials.gov (NCT_05375409, 2022–05-11) and was approved by the Institutional Review Board (KY2017-018–02) of Beijing Tiantan Hospital. Written

informed consent was obtained from all participants in this study.

The inclusion criteria for patients with frontal glioma were as follows: (1) were right-handed Han Chinese aged > 18 years, (2) spoke Chinese, (3) were scheduled to undergo elective craniotomy, (4) had histopathologically confirmed primary unilateral frontal glioma according to the 2016 World Health Organization (WHO) criteria (Louis et al., 2016), (5) had no evidence of a shift in midline structures because of mass effects on the lesion or peritumoral edema, as confirmed by MRI, and (6) had an anticipated length of stay of at least 3 days. The exclusion criteria were as follows: (1) recurrent glioma; (2) a history of cerebrovascular disease, head trauma, chemotherapy, or radiotherapy; (3) a history of drug or alcohol abuse or substance abuse; (4) a history of dementia or neuropsychiatric illness; (5) blindness, deafness, and/or sensory and mixed aphasia; (6) pregnancy or lactation; (7) contraindications for participating in an MRI study; and (8) the presence of delirium before surgery. Patient characteristics, including age, sex, education level, and grade and location of glioma, were recorded.

Participants completed an initial preoperative MRI scan one day before surgery. After surgery, patients were visited twice daily by trained researchers to diagnose delirium. If POD occurred, follow-up MRI was performed within 24 h of delirium onset. Patients who did not develop delirium by the seventh postoperative day were classified as the non-POD group, and follow-up MRI was performed 7 or 8 days after surgery. This study aimed to explore the structural and functional changes in the VN before surgery and during POD episodes through longitudinal neuroimaging data analysis.

Assessment of POD

POD was diagnosed by the Confusion Assessment Method (CAM) (Inouye et al., 1990). Delirium was evaluated twice a day on postoperative days 1–7 by two trained investigators. The patients were assigned to the POD group if delirium was diagnosed at any point in the first seven postoperative days; otherwise, they were assigned to the non-POD group. In addition, the severity of delirium was assessed by the Confusion Assessment Method-Severity (CAM-S), with scores ranging from 0 to 19 (19 = most severe) (Vasunilashorn et al., 2016).

Neuropsychological assessments

All participants completed preoperative neurocognitive assessments that were administered and scored by two experienced neuropsychologists within 1 week prior to their operation. The battery of neuropsychological tests included the following 14 tasks across global cognition and five cognitive domains: (1) global cognitive screening, assessed by the Mini-Mental State Examination (MMSE) and Montreal Cognitive Assessment (MoCA) (Beijing version); (2) processing speed/attention, assessed by the Digit Span Forward subtest of the Wechsler Adult Intelligence Test-Revised Chinese version (WAIS-RC), the Digit Symbol subtest of the WAIS-RC, the Trail Making Test A (TMT-A) and the Stroop Color Word Test (modified version) (SCWT) Part A; (3) executive function, assessed by the Chinese Version of Trail Making Test B (TMT-B) and the SCWT Part C; (4) memory, which consisted of verbal memory assessed by the Rey Auditory Verbal Learning Test (RAVLT), including the sum of trials 1 to 5 and delayed recall and recognition, and visual memory assessed by the delayed recall (30 min) subtest of the Rey-Osterrieth complex figure (ROCF); (5) language ability, assessed by the Semantic Category Verbal Fluency Test (animal) and the Boston Naming Test (BNT); and (6) visuospatial skill, assessed by the copy subtest of the ROCF and the Clock Drawing Test (CDT). The raw scores of all the cognitive tests were recorded.

Brain imaging data acquisition

The MRI data were acquired on a Philips 3.0 T MRI scanner at the MR Research Center of Beijing Tiantan Hospital. All the subjects were instructed to relax, keep their eyes closed, and not think about anything during the scan. The structural T1-weighted images were acquired with the following parameters: axial magnetization prepared rapid gradient echo (MPRAGE) sequence; repetition time (TR) = 6.5 s; echo time (TE) = 3 ms; flip angle (FA) = 8°; field of view (FOV) = 256 × 256 mm^2; matrix size = 256 × 256; voxel size = 1 × 1 × 1 mm^3; and total duration = 180 s. Resting-state fMRI (rs-fMRI) images were collected with the following parameters: TR = 2000 ms, TE = 30 ms, flip angle = 90°, slice number = 40, voxel size = 3 × 3 × 4 mm^3, and total duration = 360 s. All patients underwent two MRI scans (before and after surgery) with identical scanning parameters.

Brain imaging data preprocessing

Structural images were processed using Computational Anatomy Toolbox 12 (CAT 12, Version 12.7, r1700) with MATLAB (MathWorks, Inc., CA, United States). Voxel-based morphometry (VBM) was used to analyze individual structural images for brain volume quantification. First, skull stripping and bias-field correction were performed, and the whole brain was subsequently segmented into gray matter (GM), white matter (WM) and cerebrospinal fluid (CSF). Next, the segmented GM and WM were normalized to the MNI space (voxel size: 2 × 2 × 2 mm^3) using the optimized shooting algorithm and then smoothed with a 4-mm full width at half-maximum (FWHM) Gaussian kernel. Normalization of the brain to the MNI stereotactic space is crucial in

the presence of tumors or cavities of resection. Based on our experience and the findings of previous studies, a DARTEL approach was used without tumor masking (Ripollés et al., 2012).

To anatomically define the lesions of each patient, we normalized the original FLAIR images to the MNI template with SPM12 using a spatial resolution of $1 \times 1 \times 4$ mm. The lesion was traced manually with MRIcron software (Rorden, 2017). The lesion overlap maps are displayed in Fig. 1. Tumor volumes were automatically calculated with MRIcron from the lesion drawing.

The rs-fMRI data were preprocessed using the Data Processing and Analysis of Brain Imaging (DPABI) toolbox (http://rfmri.org/DPABI). The preprocessing steps included removal of the first 10 scans, slice-timing correction, realignment, spatial normalization to the EPI template (voxel size $2 \times 2 \times 2$ mm^3), regression of nuisance covariates (including 24 head motion parameters, linear trend, and WM/CSF signal), 0.01 ~ 0.1 Hz bandpass filtering, smoothing (FWHM: 4 mm) and scrubbing (deletion of time points with a framewise displacement [FD] > 0.2 in addition to the two prior time points and one subsequent time point). Scrubbing is an important procedure for data quality control in functional connectivity analysis (Power et al., 2012, 2014), and the discarded volumes for each group were as follows: pre-surgical discarded volumes in POD group was 7.0 (12.0), post-surgical discarded volumes in POD group was 12.0 (26.7), pre-surgical discarded volumes in non-POD group was 13.0 (20.7) and post-surgical discarded volumes in non-POD group was 9.3 (14.2). There was no significant difference in discarded volume number between POD and non-POD groups as well as pre-surgical and post-surgical group ($P > 0.05$). Then, regions showing significant differences in GM volume between the POD and non-POD groups were selected as seeds for calculating functional connectivity (FC). Pearson's correlation coefficients were computed between the mean time series of the seed and the remaining vox8els of the whole brain. To improve normality, the correlation coefficients were transformed into Fisher's z scores.

Statistical analysis

This was a secondary study of a protocol, therefore there was no a priori statistical plan for our specific analysis. The sample size was based on general estimates for the neuroimaging marker, which was examined within the previous cohort study. For neuroimaging markers, the previous study was initially aiming for effect sizes (Hedges g) of 0.5–1.5. An incidence of 30% for POD and a 5% drop-out rate initially expected. Accordingly, an effect size of 0.5 to yield 80% power ($\alpha = 5\%$, two-sided) approximately a sample size of 50. All variables had < 5% missing data, and we performed

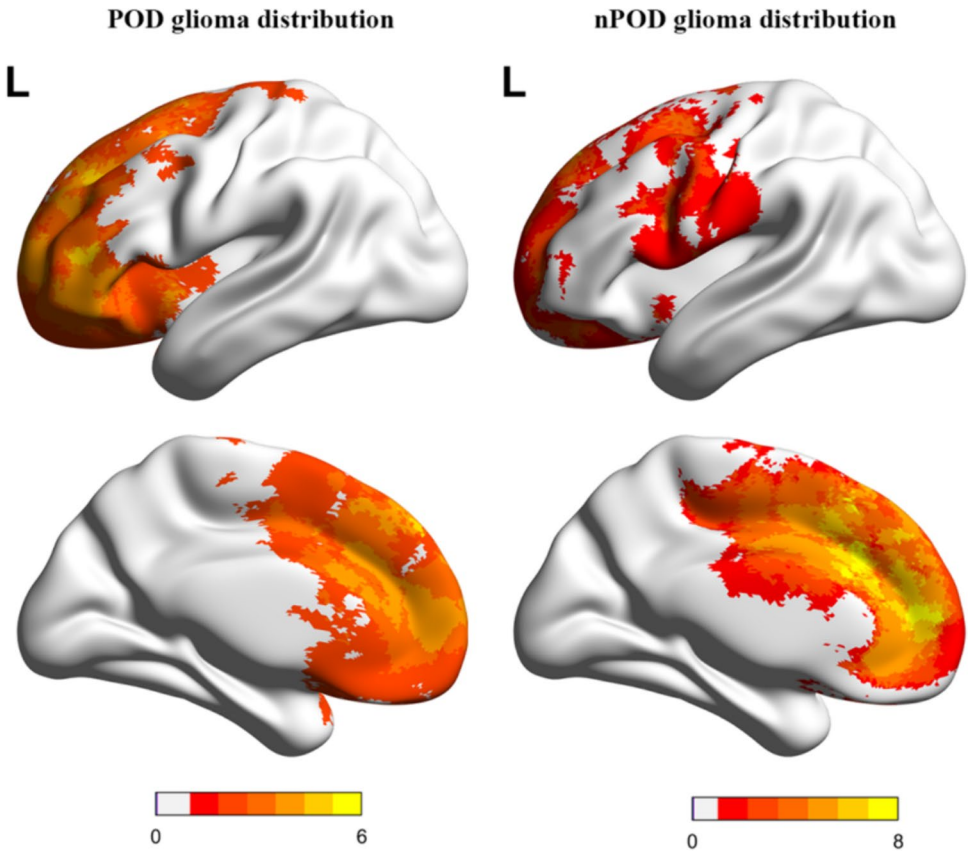

Fig. 1 Glioma distribution map for POD and non-POD group. The color bar indicates the number of patients who had tumors at that location

a complete case analysis where patients with missing data were excluded for all analyses.

All the statistical analyses of the clinical data were performed using SPSS 22.0 (IBM, Armonk, New York). Continuous variables are expressed as the mean (SD), and categorical data are expressed as proportions. Two-sample t tests and χ^2 tests were performed to compare the demographic and neurocognitive characteristics between the POD group and the non-POD group. The threshold for statistical significance was set at $p < 0.05$.

The statistical analysis of the multimodal MRI data was also performed with DPABI software. One-sample t test were performed to determine group-level significance at each condition (presurgery state, postsurgery state and postsurgery non-POD state), and two-sample t tests were also conducted to examine between-group differences. The effects of age, sex, education, tumor volume, and total intracranial volume were eliminated by being used as covariates in the analyses. The statistical thresholds for GMV were set as False discovery rate (FDR) correction ($P < 0.05$, voxel significance $P < 0.01$ and cluster size > 20) for multiple comparison. The significance level for FC was set with a Gaussian random field (GRF) correction ($P < 0.05$, voxel significance $P < 0.001$, cluster size > 20) for multiple comparisons. We also conducted the two-factor repeated-measure analysis of variance (ANOVA) and post-hoc test to identify the main effects of group (POD versus non-POD) and time-point (presurgery state versus postsurgery state). We firstly analyzed the whole brain GM volume (GMV) alteration between POD and non-POD group. However, the analysis of whole brain GMV did not show any significantly different brain regions between groups, probably because of small sample size. Then, according to our hypothesis, we selected the VN as the region of interest, which was chosen from the Brainnetome Atlas based on the YEO network template as an explicit mask, to further compare the alteration of GMV with the same statistical thresholds. The presurgery regions with significant GMV differences were subsequently selected as the seeds for calculating FC alterations between the seed regions and whole brain between groups. We calculated effect size for volumetric and FC differences between groups using9 the t tests. Effect size was reported in Cohen's d (0.2–0.5 = small, 0.5–0.8 = medium, > 0.8 = la rge). Finally, to avoid "double dipping" (Kriegeskorte et al., 2009), in which statistical tests are performed only on the significant neuroimaging indices, we performed regression analysis to examine the association between potential neuroimaging biomarkers and POD. We conducted the logistic regression model for each potential neuroimaging biomarkers. Variables with a P value less than 0.1 in the univariable analyses and with clinical significance were entered into the multivariable analysis in a stepwise forward manner requiring a P value less than 0.05 to remain. Odds ratios (ORs) and 95% CIs were calculated to assess the independent contributions of significant variables.

Results

Clinical characteristics

Table 1 showed the baseline clinical characteristics and neurocognitive assessment results of all participants, including 12 patients with POD and 24 non-POD patients. The tumors in all the patients were located in the left frontal lobe, and the tumor distributions in the POD and non-POD groups are shown in Fig. 1. Specifically, the 25th, 50th, and 75th quantiles of the glioma volume and the glioma volume range were as follows: POD group: [19.2 ml, 74.7 ml, 144.3 ml], range: 8.2 ml—260.0 ml; non-POD group: [11.8 ml, 24.1 ml, 78.8 ml], range: 4.3 ml – 129.4 ml. No significant differences were found in sex ($P = 0.99$), years of education ($P = 0.49$), duration of surgery($P = 0.74$), preoperative frailty($P = 0.36$),tumor volume ($P = 0.07$) or tumor grade ($P = 0.45$) between the POD and non-POD groups, although a significant difference was observed in age ($P = 0.015$). Compared to non-POD patients, patients with POD had significantly greater TMT-A scores, which were used to evaluate attention ($P = 0.04$).

Cross-sectional GMV comparison between POD patients and non-POD patients

The analysis of whole brain GMV without mask did not show any significantly different brain regions between groups, both before and after surgery. However, as shown in Fig. 2, when selecting the VN as the region of interest, both before and after surgery, between-group GMV comparisons revealed that POD patients had a smaller GMV in the right fusiform gyrus (before: Cohen's d = 0.858, t-test = 2.12, FDR $p = 0.007$; after: Cohen's d = 0.912, t-test = 1.19, FDR $p = 0.01$), and compared with presurgery data, patients exhibited no significant difference both in postoperative non-delirium state and postoperative state(t-test = 1.10, FDR $P = 0.21$). In the ANOVA of GMV of fusiform, a main group effect was found in right fusiform gyrus (x/y/z = 36/–69/-20; size = 121mm^3), in which the GMV was significantly smaller in the POD group than in the non-POD group (t = 5.387, $p = 0.001$). However, in this analysis, we did not find a main effect of time or a group × time interaction effect (F = 21.47, $p = 0.07$). Post hoc analysis showed that there were no significant GMV differences in any intragroup comparison, and significant GMV alterations were detected between the POD and non-POD groups both before surgery (0.181 [0.018] vs. 0.207 [0.022], FDR$p = 0.001$) and after surgery

Table 1 Comparison of demographic and cl11inical variables between the POD group and non-POD group (univariable analysis)

Variables	POD group ($n=12$)	Non-POD group ($n=24$)	P value
Age (years)	47.8 (10.7)	39.3 (8.8)	0.02*
Gender (female/male)	4/8	8/16	0.99
Education (years)	13.2 (3.8)	13.1 (3.7)	0.49
Preoperative frailty (scores)	0.08 (0.28)	0.20 (0.51)	0.36
Duration of surgery (min)	166.7 (41.1)	160.8 (60.5)	0.74
Tumor grade (low grade/high grade)	7/5	18/6	0.45
TIV (mm^3)	1499.2(129.3)	1471.2 (124.8)	0.63
Tumor volume (cm^3)	87.1 (78.8)	42.2 (78.5)	0.07
Fractions of glioma in contrast to the whole brain (%)	4.07 (4.63)	3.51(2.78)	0.70
Preoperative mean FD	0.078 (0.0378)	0.0915 (0.0585)	0.42
Postoperative mean FD	0.0973 (0.0773)	0.0799 (0.0532)	0.49
Preoperative cognition			
Global cognitive screening			
MMSE score	25.2 (3.3)	26.3 (3.0)	0.41
MoCA score	21.1 (3.8)	23.3 (4.0)	0.44
Processing speed/attention			
DST	12.3 (2.4)	13.3 (2.7)	0.63
TMT-A	54.3 (29.3)	33.2 (12.2)	0.04*
SCWT Part A	20.3 (5.2)	17.2 (5.1)	0.20
Executive function			
TMT-B	113.8 (69.7)	74.0 (44.2)	0.22
SCWT Part C	38.6 (11.8)	34.8 (12.0)	0.69
Verbal memory			
Sum of trials 1–5 of RAVLT	44.9 (13.4)	49.8 (9.8)	0.70
Delay recall of RAVLT	8.5 (4.0)	10.5 (3.1)	0.60
Visual memory			
Delay recall of ROCF	15.4 (7.3)	17.6 (9.1)	0.66
Language ability			
BNT	23.0 (3.6)	24.4 (2.9)	0.36
Visuospatial skill			
CDT	7.5 (2.5)	7.9 (2.8)	0.84

The values are presented as the number of study participants or mean (SD) unless otherwise indicated

mean FD is the mean frame-wise displacement for in-scanner head motion

TIV total intracranial volume, *MMSE* Mini-Mental State Examination, *MoCA* Montreal Cognitive Assessment, *DST* Digit Span Test, *FD* Framewise displacement, *RAVLT* Rey Auditory Verbal Learning Test, *TMT* Trail Making Test, *BNT* Boston Naming Test, *CDT* Clock Drawing Test, *SCWT* Stroop Color Word Test

(0.176 [0.020] vs. 0.206 [0.023], FDRp = 0.001) (as shown in Fig. 3).

Both before and after surgery, between-group GMV comparisons revealed that POD patients had the significantly smaller GMV in the right fusiform gyrus (x/y/z = 36/–69/-20; size = 121mm3). Compared to non-POD group ($n=24$), Before surgery, the blue cluster shows smaller GMV of right fusiform gyrus in the POD group ($n=12$) (Cohen's d = 0.858, t-test = 2.12, FDR $p=0.007$); and after surgery, the blue cluster also shows smaller GMV of right fusiform gyrus in the POD group ($n=12$) (Cohen's d = 0.912, t-test = 1.19 FDR $p=0.01$). The effects of age, sex, education, tumor volume, and total intracranial volume were eliminated by being used as covariates in the analyses. The statistical thresholds for GMV were set as False discovery rate (FDR) correction ($P<0.05$, voxel significance $P<0.01$ and cluster size > 20) for multiple comparison.

Statistical analyses were performed using two-factor repeated-measure analysis of variance (ANOVA), group (POD and non-POD) repeated over time point (presurgery and postsurgery) followed by post hoc comparison with False Discovery Rate (FDR) correction (voxel $p<0.01$ and

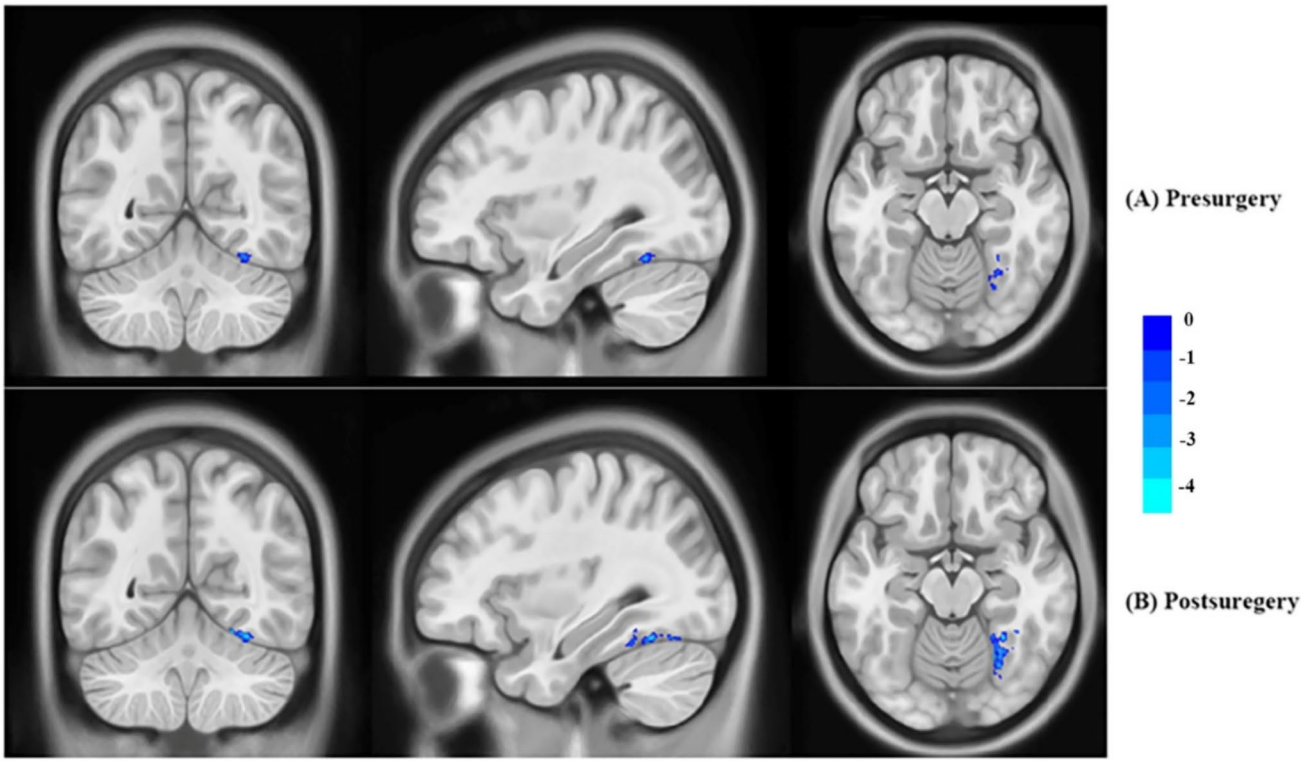

Fig. 2 Cross-sectional brain volume alterations between POD patients and non-POD patients

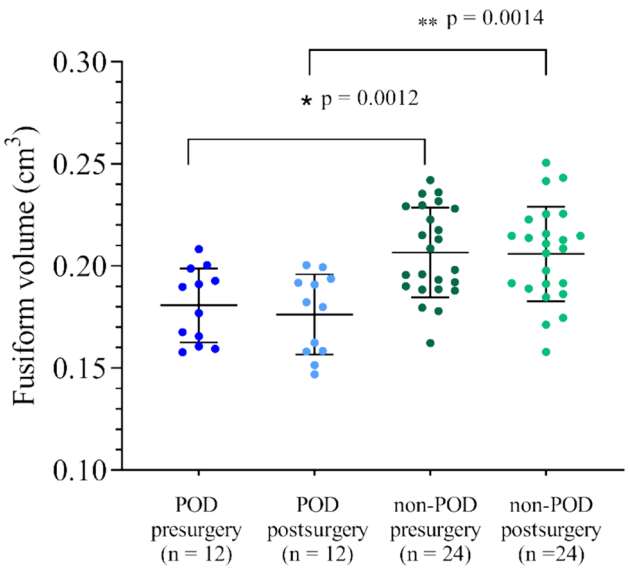

Fig. 3 Presurgical and postsurgical volumes of the right fusiform gyrus in POD and non-POD patients. POD: postoperative delirium

cluster size > 20) for the multiple comparison. MRI measurements were adjusted for age, sex, education, tumor volume, and total intracranial volume. Significance with two-sided $p < 0.05$ were considered.

Compared to the non-POD group, there were significant decreased fusiform volume in the POD group both before surgery (0.181 [0.018] vs. 0.207 [0.022], $P = 0.001$) and after surgery (0.176 [0.020] vs. 0.206 [0.023], $p = 0.001$), and there were no significant GMV differences in any intra-group comparison.

Cross-sectional seed-based FC comparison between POD patients and non-POD patients

As shown in Fig. 4, between-group GMV comparisons revealed that before surgery, POD patients exhibited decreased FC between the right fusiform gyrus and the left lingual gyrus and lateral occipital cortex (belonging to the visual network) (Cohen's d = 0.810, t-test = 1.47, GRF $P = 0.03$); and after surgery, POD patients presented increased FC between the right fusiform gyrus and right inferior parietal lobule (IPL, A40rv, rostroventral area 40, belonging to the ventral attention network [vAN]) (Cohen's d = 0.859, t-test = 2.87, GRF $P = 0.002$). For the FC between right fusiform gyrus and the left lingual gyrus and lateral occipital cortex, there was no significant interaction effect between group and time point (F = 10.51, $p = 0.09$). Post hoc analysis showed significantly decreased FC between the right fusiform gyrus and the left lingual gyrus and lateral occipital cortex in POD patients before

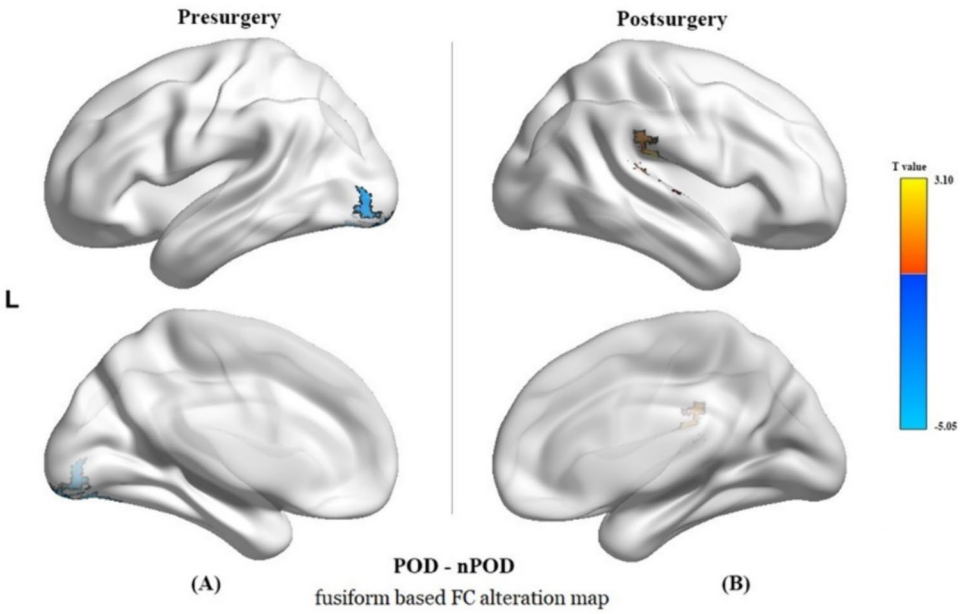

Fig. 4 Cross-sectional differences in fusiform-based FC between POD patients and non-POD patients

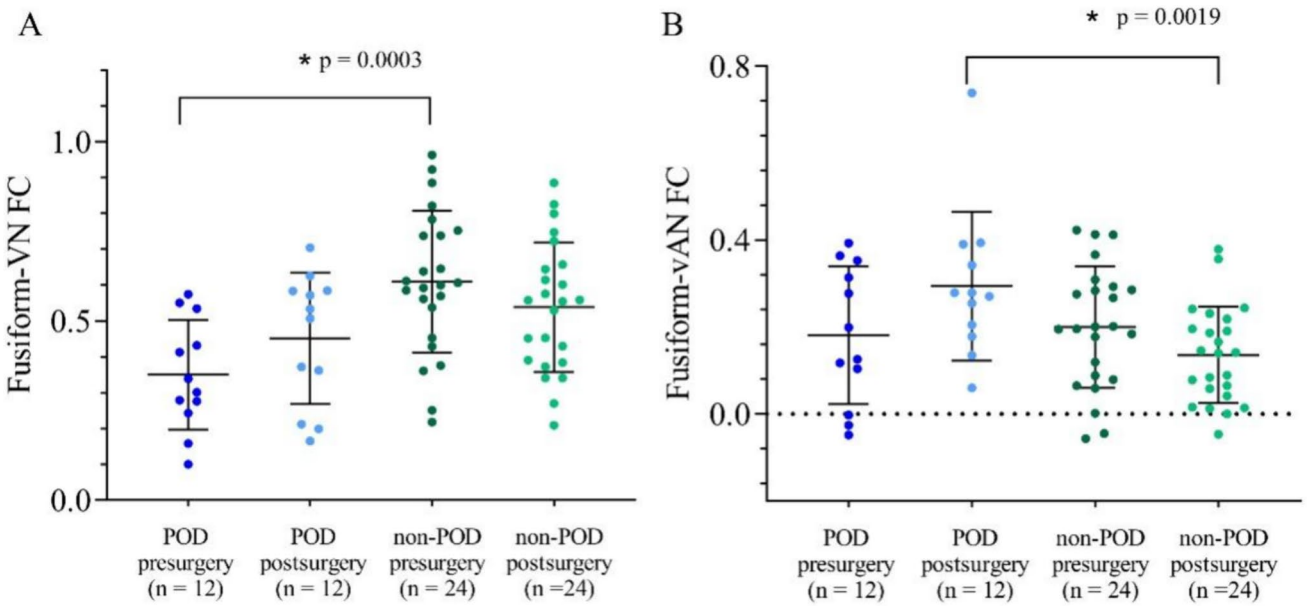

Fig. 5 Preoperative and postsurgical FC alterations in POD and non-POD patients. FC: functional connectivity; vAN: ventral attention network; VN: visual network; POD: postoperative delirium

surgery (0.351 [0.153] vs. 0.610 [0.197], $p < 0.001$), and no significant difference for controls between two time points (t = 4.29, GRF$p = 0.09$) (Fig. 5). For the FC between right fusiform gyrus and right IPL, there was also no significant interaction effect between group and time point (F = 7.41, $p = 0.08$). Post hoc analysis showed significantly increased FC between the right fusiform gyrus and the right IPL in POD patients after surgery (0.538 [0.180] vs. 0.452 [0.184], GRF$p = 0.002$), and no significant difference for controls between two time points (t = 6.72, GRF$p = 0.11$) (Fig. 5).

Compared to non-POD ($n = 24$), before surgery, blue cluster shows decreased FC between the right fusiform gyrus and the left lingual gyrus and lateral occipital cortex in POD group ($n = 12$) (Cohen's d = 0.810, t-test = 1.47, GRF $P = 0.03$) (A), and after surgery, orange cluster shows increased FC between the right fusiform gyrus and right inferior parietal lobule in POD group ($n = 12$) (Cohen's

d = 0.859, t-test = 2.87, GRF $P = 0.002$)(B).The effects of age, sex, education, tumor volume, and total intracranial volume were eliminated by being used as covariates in the analyses. The statistical thresholds for GMV were set as Gaussian random field (GRF) correction ($P < 0.05$, voxel significance $P < 0.001$, cluster size > 20) for multiple comparison.

Statistical analyses were performed using two-factor repeated-measure analysis of variance (ANOVA), group (POD and non-POD) repeated over time point (presurgery and postsurgery) followed by post hoc comparison with Gaussian random field (GRF) correction ($P < 0.05$, voxel significance $P < 0.001$). MRI measurements were adjusted for age, sex, education, tumor volume, and total intracranial volume. Significance with two-sided $p < 0.05$ were considered.

A: Comparison of FC between the fusiform gyrus and visual network (VN) between POD patients and non-POD patients. Compared to the non-POD group, there was the significantly decreased FC between the fusiform gyrus and VN between in the POD group before surgery (0.351 [0.153] vs. 0.610[0.197], $p < 0.001$).

B: Comparison of FC between the fusiform gyrus and ventral attention network (vAN) between POD patients and non-POD patients. Compared to the non-POD group, there was the significantly increased FC between the fusiform gyrus and vAN between in the POD group before surgery (0.538 [0.180] vs. 0.452 [0.184], $p = 0.002$).

Correlations between neuroimaging biomarkers and POD incidence

In the model 1, in the univariable analysis, age (crude OR = 1.103, 95% CI [1.012–1.201], $P = 0.02$) was significantly related to POD(Table 2), and in the multivariable analysis, age (OR = 1.112, 95% CI [0.786–1.227], $P = 0.04$) was found to be independent variables for POD (Table 2). In the model 2, in the univariable analysis, age (crude OR = 1.103, 95% CI [1.012–1.201], $P = 0.02$) and fusiform-VN FC (crude OR = 0.001, 95% CI [0.001–0.077], $P = 0.02$) was significantly related to POD(Table 3), and in the multivariable analysis, age (OR = 1.141, 95% CI [1.015–1.282], $P = 0.03$) and fusiform-VN FC were found to be independent variables for POD (Table 3).

Table 2 Multiple logistic regression: model 1 — the association between fusiform-visual network functional connectivity and postoperative delirium

Variable	Estimated Beta	Standard Error	Univariable analysis Crude odds ratio (95% CI)	*P* value	Multivariable analysis Odds ratio (95% CI)	*P* value
Age	-0.018	0.114	1.103 (1.012–1.201)	0.02*	1.112 (0.786–1.227)	0.04*
Tumor size	0.161	0.101	1.014 (1.000–1.029)	0.16	1.174 (0.964–1.431)	0.11
TMT-A	0.621	0.450	1.067 (1.008–1.129)	0.20	1.861 (0.770–4.496)	0.17
Education	-1.633	1.144	0.929 (0.756–1.141)	0.38	0.195 (0.021–1.840)	0.15
Duration of surgery	0.051	0.041	1.002 (0.989–1.015)	0.23	1.053 (0.972–1.140)	0.21
Fusiform-volume	-302.763	183.312	0.001 (0.000–2.547)	0.12	0.001 (0.000–2.522)	0.10
Constant	37.050	22.822	0.056	0.29	0.047	0.10

CI confidence interval, *FC* functional connectivity, *TMT* Trail Making Test, *VN* visual network

Table 3 Multiple logistic regression: model 2 — the association between fusiform volume and postoperative delirium

Variable	Estimated Beta	Standard Error	Univariable analysis Crude odds ratio (95% CI)	*P* value	Multivariable analysis Odds ratio (95% CI)	*P* value
Age	0.132	0.060	1.103 (1.012–1.201)	0.03*	1.141 (1.015–1.282)	0.03*
Tumor size	0.015	0.017	1.014 (1.000–1.029)	0.37	1.015 (0.982–1.050)	0.37
TMT-A	0.057	0.051	1.067 (1.008–1.129)	0.23	1.059 (0.959–1.169)	0.26
Education	0.005	0.275	0.929 (0.756–1.141)	0.99	1.005 (0.587–1.722)	0.98
Duration of surgery	0.026	0.013	1.002 (0.989–1.015)	0.06	1.026 (0.999–1.053)	0.06
Fusiform-VN FC	-11.270	4.370	0.001 (0.001–0.077)	0.02*	0.001 (0.001–0.067)	0.01*
Constant	-5.471	3.474	0.078	0.13	0.004	0.12

CI confidence interval, *FC* functional connectivity, *TMT* Trail Making Test, *VN* visual network

*Denotes statistical significance at $p < 0.05$

Discussion

To our knowledge, so far, few studies have investigated the effect of the VN on the development of POD from a neuroimaging perspective. In a cross-sectional and longitudinal analysis of a prospective observational cohort study of frontal glioma patients, we found that the preoperative disconnectivity of the VN was associated with increased odds of developing POD.

In the present study, we performed multimodal neuroimaging comparisons and found that before surgery, frontal glioma patients with POD displayed a smaller GMV in the fusiform gyrus and a lower FC between the right fusiform gyrus and the left occipital lobe/lingual gyrus than non-POD patients. The occipital cortex and fusiform and lingual gyri are components of the primary and secondary visual cortex network, respectively. They are closely connected in the processing and transmission of visual signals. The occipital cortex, as the primary visual cortex, is responsible for receiving and processing initial visual information, such as color and contours (Ibbotson and Jung, 2020). The fusiform and lingual gyri, as important nodes of the secondary visual cortex, are responsible for further processing complex visual information and are closely associated with the process of visual memory. Previous studies have reported that these brain regions may be associated with positive memories and engagement in psychological imagination (Pearson, 2019; Spagna et al., 2021). Moreover, the fusiform gyrus is also the core area responsible for facial recognition, and several studies have shown that functional abnormalities in this region may be associated with facial hallucinations, which can explain the occurrence of hallucinatory symptoms in patients with delirium (Jonas et al., 2018; Zaragoza-Jimenez et al., 2023). We subsequently performed multivariable logistical analysis and found that, except for age, a previously reported risk factor, only preoperative fusiform-VN FC was an independent predictor of POD. In addition, the significant negative correlation between the fusiform-VN FC and the severity and duration of POD reinforces the important role of the VN in the development of POD. Therefore, our findings suggest that FC deficits in the VN might be a preexisting neural basis for POD in the frontal glioma patients. Notably, we did not find significant differences in any other important visual areas, such as the parietal lobe or temporal lobe, between the POD and non-POD groups, probably because of the relatively small sample size.

Additionally, our multivariable analysis showed that the preoperative TMT-A score was not an independent risk factor for POD in our participants, although it was significantly different between the two groups according to the univariable analysis. The TMT-A is a classic assessment method for attention. A previous study by Lammers et al. reported that the TMT-A score was associated with FC in the supplementary motor network (Lammers et al., 2020), thus revealing a potential link between the primary sensory and perceptual network and attention function. Given that inattention is the core symptom of delirium, we infer that before surgery, preexisting impairment of the VN may have a “dormant” impact on the brain regions that support attention and become the neural basis of inattention-related symptoms during episodes of POD in our subjects.

The analysis of longitudinal neuroimaging data revealed that there were no significant differences in fusiform GMV alterations in any intragroup comparison, perhaps because the brain structure in nonoperative areas cannot change within the short interval between two MRI scans (one week). The study also revealed that, in frontal glioma patients with POD, compared to the preoperative data, the FC between the right fusiform gyrus and a critical node of the ventral attention network (vAN), the IPL, was greater after surgery. These results suggest that the preoperative preexisting damaged VN suffered from incremental deterioration under perioperative stress, subsequently affecting the internetwork FC between the VN and vAN. The dedifferentiation hypothesis proposed by Jockwitz (Jockwitz et al., 2017) could explain our postoperative data since poorer attention function seems to be associated with functional desegregation of cortical areas involved in higher cognitive function and visual areas. Song et al. reported that the FC between the fusiform gyrus and the vAN is related to visual spatial attention processing and could affect attention to significant events (Song et al., 2020). Therefore, during an episode of POD, the change in FC between the fusiform gyrus and the IPL may be closely related to the symptom of inattention. The increased FC between the fusiform gyrus and vAN seems to be a transient compensatory mechanism for the disrupted VN. Given that compensatory hyperconnection responses after the disruption of a network usually occur in degenerative disorders, this overuse of brain resources may be linked to long-term cognitive decline after an episode of delirium (Oh et al., 2019). Moreover, it is worth noting that the abnormal preoperative FC within the VN disappeared during POD. This may be due to the modulating role of the frontal lobe on the functional interaction between the primary and secondary visual cortices. Therefore, when frontal lobe tumors are removed, the abnormal interactions between the primary and secondary visual cortices may be partially restored, resulting in the FC within the VN approaching normalization after surgery.

In recent years, researchers have begun to pay attention to the regulatory role of the VN in neuropsychiatric disorders (Chen et al., 2019; Wu et al., 2023). Visual processing, which serves as the most critical initial step in the brain's communication with the outside world, may impact higher-order cognitive functions in a "bottom-up" manner (Dong et al.,

2023; Martinez et al., 2020). For instance, a study conducted by Wang et al. showed that in patients with schizophrenia, decreased FC between the VN and the SN may cause difficulties in the selection of external visual information and subsequently result in symptoms of apathy (Wang et al., 2021). Therefore, we propose that the breakdown of the processing and transmission of external visual signals could overwhelm the brain with a substantial amount of redundant unselective external information and could lead to impaired higher-order cognitive functions during POD episodes.

Several limitations of this study need to be considered. First, the sample size was relatively small, with only 36 frontal glioma patients, due to the strict inclusion criteria. The small sample size might have affected the results of the whole-brain voxelwise analysis; therefore, we selected only the potential neuroimaging biomarker of the VN as the seed to calculate FC alterations. Future studies with larger sample sizes are needed to validate the findings and enhance the generalizability of the results. Second, in our work, the mean glioma volume was not significant different between POD and non-POD groups, and we have adjusted the effect of tumor volumes by multiple logistic regression. However, the median, upper quartile and maximum tumor volume are 2–3 times larger in POD group compared the non-POD group. Therefore, tumor volume may still be a potential source of bias. We should further verify our opinion in non-brain injured patients in the future research. Third, the inclusion criteria had no restriction on sex. However, there were only 4 female patients with delirium in the POD group, and the small sample size could have contributed to this bias. Notably, the study by Schenning et al. suggested that sex predisposes older patients to postoperative cognitive dysfunction (Schenning et al., 2019). Therefore, the influence of sex on POD should be explored in the future. Fourth, multimodal imaging data after patients recovered from delirium were lacking. These data could provide further confirmation of the contribution of VN abnormalities to the occurrence of POD. Fifth, a smoothness kernel of 6–8 mm FWHM is recommended for functional images (Candemir, 2023); however, a 4 mm FWHM kernel was used in this study, and future studies are needed to ascertain the influence of the smoothness kernel. Sixth, the scrubbing procedure without interpolation in the rs-fMRI preprocessing may influence the calculated FC, which needs future study to decide the best selection for motion control (Parkes et al., 2018).

Conclusion

In the present study, in frontal glioma patients with POD, the functional disconnectivity in the VN might be highly involved in the development of POD. Our study provides the neuroimaging evidence that the VN deficits may constitute an important factor in the neural pathological basis of POD, and contribute to the understanding of underlying mechanism of POD.

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Author contributions HH, GZ and BJ designed the study. HL, XZ and GZ collected the data. HH, BJ, GZ, JC and BQ analyzed the datasets and interpreted the results. GZ, HH, BQ, HL and BJ wrote and edited the manuscript. HH GZ and BJ provided the foundation and support. All the authors read and approved the final manuscript.

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Data availability No datasets were generated or analysed during the current study.

Declarations

Ethical approval The experiment was approved by the Institutional Review Board (KY2017-018–02) of Beijing Tiantan Hospital and registered with ClinicalTrials.gov (NCT_05375409, 2022–05-11). All the experiments were performed in accordance with the principles of the Declaration of Helsinki.

Informed consent Written informed consent was obtained from all participants.

Conflict of interest The authors declare no competing interests.

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