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Original Article

Disrupted Connectivity of the Brainstem Ascending Reticular Activating System Nuclei-left Parahippocampal Gyrus Could Reveal Mechanisms of Delirium Following Basal Ganglia Intracerebral Hemorrhage

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Abstract

Background and objectives: Delirium, commonly observed in critically ill patients following intracerebral hemorrhage (ICH), is an acute neuropsychiatric disorder characterized by disturbances in attention, consciousness, and cognition. The underlying brain network mechanisms remain poorly understood. This study aimed to explore the functional connectivity (FC) of the ascending reticular activating system (ARAS) in delirium patients with basal ganglia ICH and to identify potential biomarkers for predicting delirium onset.

Methods: In this cross-sectional study, brain networkomics techniques were used to examine the FC within the ARAS in ICH patients with and without delirium. A two-sample t-test compared differences in ARAS connectivity between delirium and non-delirium groups, identifying abnormal brain regions and their corresponding FC values. Receiver operating characteristic curve analysis was then performed to evaluate the predictive value of FC for delirium onset.

Results: A significant disruption in FC between the brainstem ARAS nuclei and the left parahippocampal gyrus was observed in ICH patients with delirium. The FC strength between these regions was a reliable predictor of delirium occurrence, with an area under the curve of 0.893, indicating high predictive accuracy.

Conclusions: The disruption of FC between the brainstem ARAS nuclei and the left parahippocampal gyrus may represent a key mechanism underlying delirium pathogenesis. The strength of this connectivity could serve as a potential biomarker for predicting delirium onset. Future research should focus on strategies to restore this connectivity as a potential treatment for early reversal of delirium.

Keywords: Intracerebral hemorrhage; Basal ganglia; Delirium; Ascending reticular activating system; Parahippocampal gyrus; Functional connectivity; Mechanisms.

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Introduction

Delirium is an acute neuropsychiatric disorder characterized by impairments in attention, consciousness, and cognition. It is commonly observed in patients with critical illnesses such as stroke.[1] Delirium presents in various forms, including hypoactive, hyperactive, and mixed subtypes, with symptoms such as confusion, hallucinations, agitation, and emotional distress.[2]

Delirium significantly impacts patient outcomes, leading to prolonged hospital stays, increased mortality risk, and long-term cognitive and functional decline.[3] In patients with intracerebral

hemorrhage (ICH), the presence of delirium is associated with worse neurological outcomes, higher rates of dementia, and complications such as unintentional injuries.[4–6] Pathophysiologically, delirium results from a complex interplay of neuroinflammation, neurotransmitter imbalances, and disruptions in brain network function.[7–9] Therefore, early detection and timely intervention are crucial for improving recovery outcomes.Brain networks are essential for the efficient transmission of information, and coordination between different network modules ensures the integration of functions such as arousal, attention, and cognition. Disruption of brain network connectivity is closely linked to the development of neuropsychiatric disorders, including delirium. A systematic review of 126 studies by van Montfort and colleagues suggested that disintegration of brain networks is a common final pathway in the development of delirium.[8] The ascending reticular activating system (ARAS), a widely projecting structure connecting the cortex and subcortical regions, plays a critical role in maintaining arousal and awareness.[10] However, specific details regarding the functional connectivity (FC) of the ARAS in delirium patients remain underexplored. In particular, it is not yet known whether abnormal FC within the ARAS network could serve as a characteristic biomarker for predicting the onset of delirium.[8]

We hypothesize that abnormalities exist in the connections between the brainstem ARAS nuclei and brain regions involved in memory, cognition, or language. In this study, we constructed an extensive subcortical and subcortical projection system using the brainstem ARAS nuclei as seed points. This research aimed to investigate the FC circuits of the ARAS in patients with delirium following basal ganglia ICH, to uncover potential mechanisms of delirium, and to identify characteristic connectivity patterns that may serve as predictive biomarkers for its onset.

Materials and methods

Participants

This observational cross-sectional study follows the guidelines outlined in the Strengthening the Reporting of Observational Studies in Epidemiology statement and received approval from the Huashan Hospital Ethics Committee, affiliated with Fudan University.[11] A total of 60 participants were enrolled between October 2021 and December 2022. All participants or their families provided written informed consent prior to participation. Each participant underwent a magnetic resonance imaging (MRI) scan, completed relevant scale assessments, and had their clinical data collected.

Inclusion criteria: (1) Age 18–85 years; (2) Computed tomography or MRI confirmation of ICH in the basal ganglia region,[12] and a diagnosis of delirium confirmed by the Confusion Assessment Method Chinese revision (CAM-CR) - Diagnostic and Statistical Manual of Mental Disorders, 4th edition (assessed by trained study members)[4,5]; (3) MRI scanning performed within 24 h following the scale assessment; (4) Right-handedness (intact limbs); (5) Normal communication, work, and daily life before the onset of ICH; (6) Stable vital signs and spontaneous breathing.

Exclusion criteria: (1) Comorbid psychiatric and/or neurological disorders; (2) History of significant head trauma, ICH, and/or tumor; (3) History of substance and/or alcohol abuse and/or smoking; (4) Contraindications to MRI, such as pacemaker, metal implants, and/or claustrophobia; (5) Pregnancy; (6) Patients who remained agitated despite multiple attempts (approximately three times) during MRI scans.

Delirium assessment

An adapted version of the Confusion Assessment Method, tailored for the Chinese population, was used for quantitative evaluation. Introduced in China in 2000, the Confusion Assessment Method was revised to create the Chinese version, CAM-CR, better suited for Chinese individuals.[13] The CAM-CR includes eleven assessment items: acute onset, inattention, disorganized thinking, altered level of consciousness, disorientation, memory deficits, perceptual disturbances, psychomotor agitation or retardation, symptom fluctuations, and sleep-wake cycle alterations. Each item is rated by severity: 1 (absent), 2 (mild), 3 (moderate), and 4 (severe). A total score below 19 indicates no delirium, scores between 20 and 22 suggest possible delirium, and scores above 22 confirm a diagnosis of delirium. In this study, trained staff conducted CAM-CR assessments twice daily (morning and afternoon). Participants with an average score greater than 22 were classified as having delirium, while those with lower scores were categorized as non-delirium.

Imaging data

Data acquisition was performed after the morning CAM-CR assessment, with a repeat assessment in the afternoon; scores remained stable throughout. MRI data for all participants were obtained using a 3 T MRI scanner equipped with a standard 8-channel head coil (Discovery MR750, GE Medical Systems, Milwaukee, WI, USA). Resting-state functional MRI (rs-fMRI) data were collected using an echo-planar imaging sequence with the following parameters[14]: Repetition time (TR)/echo time (TE) = 2,000/30 ms, field of view = 240 mm × 240 mm, flip angle = 70°, matrix size = 64 × 64, slice thickness = 3.5 mm, 33 slices, and 240 volumes.

For structural imaging, 3D T1-weighted images were captured with the following parameters[14]: TR/TE = 8.16/3.18 ms, flip angle = 12°, matrix size = 256 × 256, slice thickness = 1.0 mm, inter-slice gap = 0 mm, and 168 slices.

Lesion frequency map

The lesion frequency map was created following these steps[14]: (1) The MRIcroGL software (https://www.mccauslandcenter.sc.edu/mricrogl/) was employed to delineate the location and extent of each brain lesion on the T1-weighted image, with the region identified by consensus between two experienced neurosurgeons; (2) Lesion masks generated for each patient with ICH were aligned to the Montreal Neurologic Institute (MNI) template; (3) These lesion masks were resampled to a voxel size of 1 × 1 × 1 mm^3; (4) Individual lesion masks were overlaid sequentially to produce a lesion frequency map; (5) The map was visualized in MRIcroGL, with lesion overlap frequencies represented using an appropriate color lookup table; (6) The bilateral lesion frequency map was then subtracted from the whole-brain mask, and the resulting brain mask was applied during post-processing of the rs-fMRI data.

rs-fMRI data pre-processing

Data pre-processing was conducted using the DPABI V7.0 toolbox (http://rfmri.org/DPABI) in MATLAB 2016b (https://www.mathworks.com/). The processing steps included[15]: (1) Conversion from DICOM to NIFTI format; (2) Removal of the first 10 volumes; (3) Slice timing correction; (4) Realignment of images to account for head motion (participants with translation exceeding 2.0 mm and/or rotation greater than 2° were excluded); (5) Normalization to MNI space, including lesion masks and unified segmented structural images; (6) Linear detrending; (7) Bandpass filtering (0.01–0.1 Hz). Additionally, the Friston 24-parameter head motion model was used to regress out residual noise related

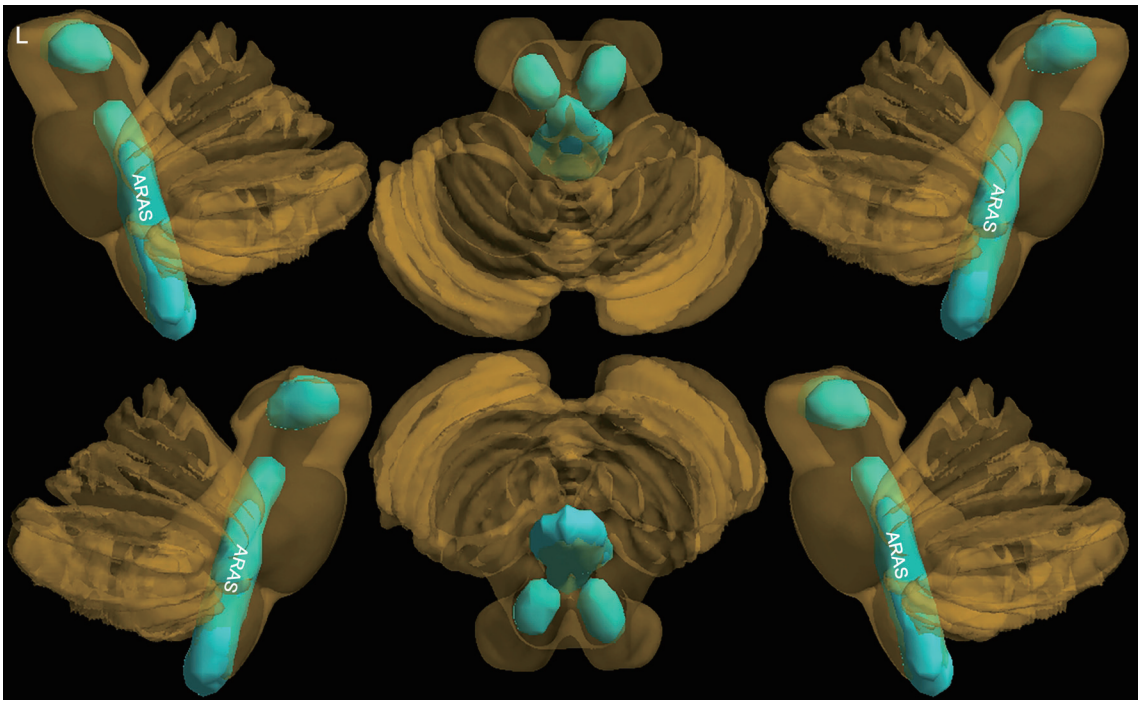

Fig. 1. Brainstem ARAS nuclei standard brain atlas diagram. ARAS, ascending reticular activating system; L, left.

to head motion and other nuisance factors (e.g., cerebrospinal fluid and white matter). Finally, spatial smoothing was applied using a Gaussian kernel (full width at half maximum = 4 × 4 × 4 mm^3).

rs-fMRI post-processing

Brainstem ARAS nuclei were constructed by overlaying previously defined brainstem templates (Fig. 1).[10] DPABI V7.0 was used to extract the average time series for the regions of interest, and Pearson's correlation analysis computed the FC between the brainstem ARAS nuclei and every voxel across the whole brain. Fisher's transformation converted the Pearson correlation coefficient (r) into a z-score. A voxel-level two-sample t-test with covariate adjustment was performed within the brain mask, controlling for cerebrospinal fluid, white matter, head motion coefficient, age, gender, and lesion volume. To correct for multiple comparisons, the AlphaSim program was applied with a cluster-level threshold of $p < 0.05$ and a minimum cluster size of 154 voxels. The z-score normalization of functional connectivity (zFC) signals corresponding to brain regions showing differences between delirium and non-delirium groups were extracted, followed by delirium patient identification analysis.

Statistical analysis

Statistical analyses were performed using MedCalc (https://www.medcalcsoftware.com/) and GraphPad Prism 9.5 (https://www.graphpad.com/). The Kolmogorov-Smirnov test assessed normality. For normally distributed data (mean ± standard deviation), inter-group comparisons were performed using a two-sample t-test. Otherwise, the Mann-Whitney U test was applied (median and quartiles). Categorical variables were analyzed using the Chi-square test. The diagnostic performance for delirium was initially evaluated using receiver operating characteristic (ROC) curve analysis. A *p*-value of < 0.05 was considered statistically significant.

Results

Baseline characteristic

A total of 60 patients with ICH in the basal ganglia region were initially enrolled in the study. However, 18 participants were excluded due to excessive head motion during scanning, and an additional nine were excluded due to image artifacts. Consequently, 33 patients remained eligible for analysis, including 15 diagnosed with delirium (Fig. 2). The detailed demographic and clinical characteristics of the delirium and non-delirium groups are presented in Table 1. All participants were right-handed, with 18 patients (54.5%) having right hemisphere lesions. The average age was 55.06 years, and the onset-to-investigation interval ranged from three to 47 days. There were no significant differences between the two groups in terms of gender, onset-to-investigation interval, or lesion hemisphere ($p > 0.05$). However, significant differences were observed in age ($p = 0.009$), lesion volume ($p = 0.010$), and CAM-CR score ($p < 0.001$).

Lesion masks and features

To ensure accurate hematoma segmentation, manual segmentation was performed, and individual lesion masks were generated for each of the 33 patients. The overlay of lesions—18 in the right hemisphere and 15 in the left is shown in Figure 3, illustrating their distribution within the basal ganglia and thalamus regions. Notably, the peak coordinates of the bilateral lesions were located near the lentiform nucleus (MNI coordinates: x/±24, y/-4, z/4).

FC disruption in the left parahippocampal gyrus among delirium patients

Results from a two-sample t-test (T = −4.356) revealed that patients with delirium exhibited significantly disrupted FC between the brainstem ARAS nuclei and the left parahippocampal gyrus,

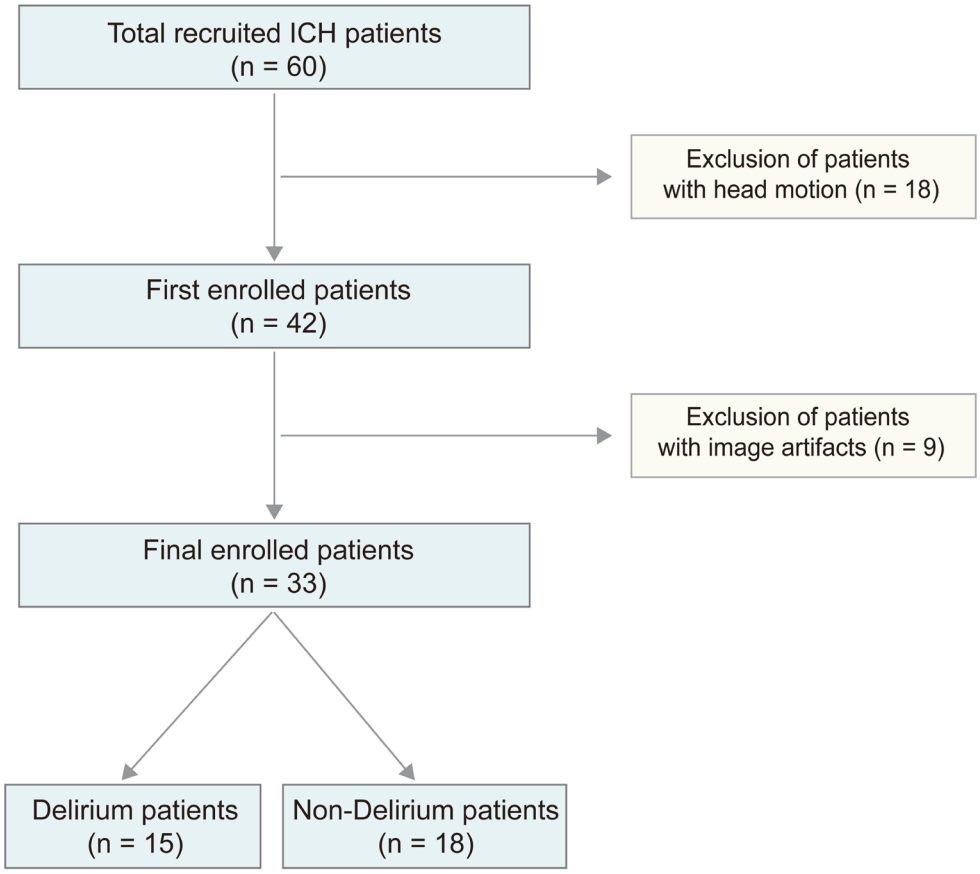

Fig. 2. Patient enrollment flowchart. ICH, intracerebral hemorrhage.

compared to non-delirious patients (AlphaSim corrected, cluster size > 154 voxels, $p < 0.05$; MNI coordinates: x/-24, y/0, z/-30; Fig. 4). For additional details on brain regions and coordinates, please refer to the File S1.

Delirium patient identification

First, we extracted the zFC values corresponding to the identified differential brain region (left parahippocampal gyrus) and performed inter-group quantitative analysis, with results displayed in Figure 5a. Subsequently, ROC analysis was performed. The results indicated that zFC values between the brainstem ARAS nuclei and the left parahippocampal gyrus can effectively identify delirium patients [area under the curve (AUC) = 0.893; Fig. 5b]. These findings suggest that FC intensity between the brainstem ARAS nuclei and the left parahippocampal gyrus may serve as a biomarker for early screening and identification of potential delirium cases.

Discussion

This study suggests that the disconnection between the brainstem ARAS nuclei and the left parahippocampal gyrus may be a key factor in the onset of delirium. Further analysis indicates that the

Table 1. Baseline features of patients with ICH

Terms	All patients	Delirium	Non-delirium	t/χ^2-value	*p*-value
Age, years	55.06 ± 13.33	61.53 ± 11.51	49.67 ± 12.56	2.806	0.009
Gender, male (%)	18 (54.5)	8 (53.3)	10 (55.6)	0.000	1.000
Hand dominance, right (%)	33 (100.0)	15 (100.0)	18 (100.0)	-	-
Onset to investigation interval, d	15.03 ± 9.77	13.60 ± 6.48	16.72 ± 11.85	−0.912	0.369
Lesion hemisphere, right (%)	18 (54.5)	5 (33.3)	13 (72.2)	3.545	0.060
Lesion volume, ml	24.04 ± 9.17	28.41 ± 7.49	20.39 ± 9.00	2.747	0.010
CAM-CR	22.48 ± 8.16	29.53 ± 6.00	16.61 ± 3.91	7.169	<0.001

Continuous variables are presented as mean ± standrad deviation; categorical variables as number (percentage). CAM-CR, Confusion Assessment Method–Chinese Revision; ICH, intracerebral hemorrhage.

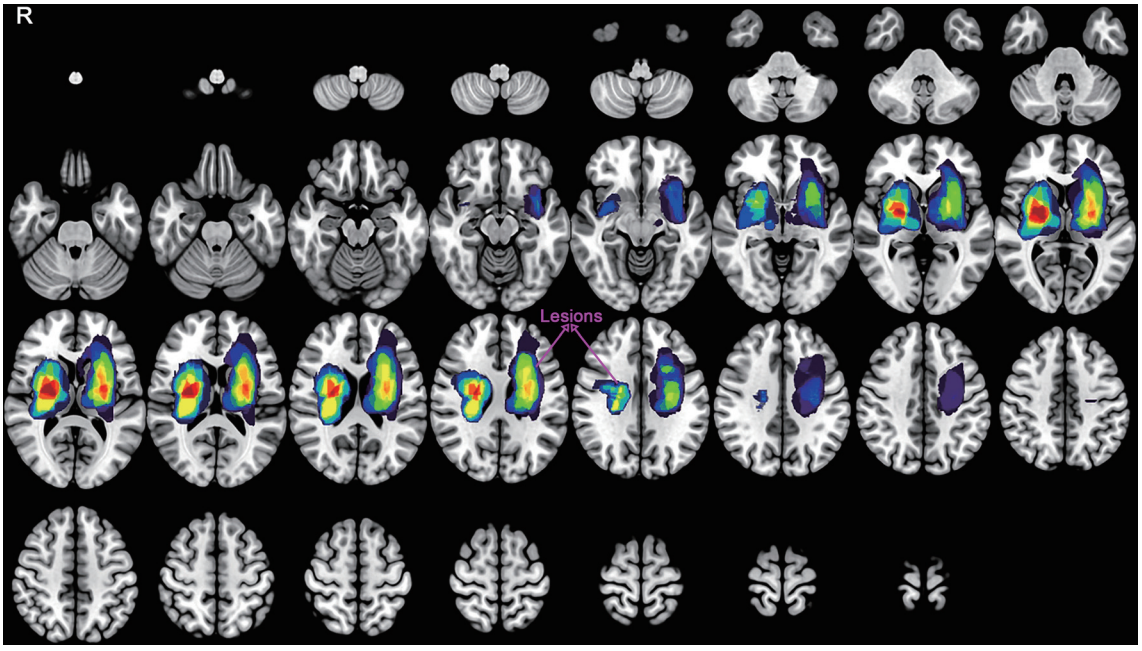

Fig. 3. The frequency overlap map of ICH lesions. ICH, intracerebral hemorrhage; R, right.

strength of the FC between the brainstem ARAS nuclei and the left parahippocampal gyrus may serve as a biomarker for predicting the occurrence of delirium.

The ARAS is an important neural network that maintains arousal and consciousness.[10] It controls alertness, attention, cognitive function, and emotional states by regulating neural signal transmission from the brainstem to the cerebral cortex. The core components of the ARAS include the midbrain, pons, and medulla

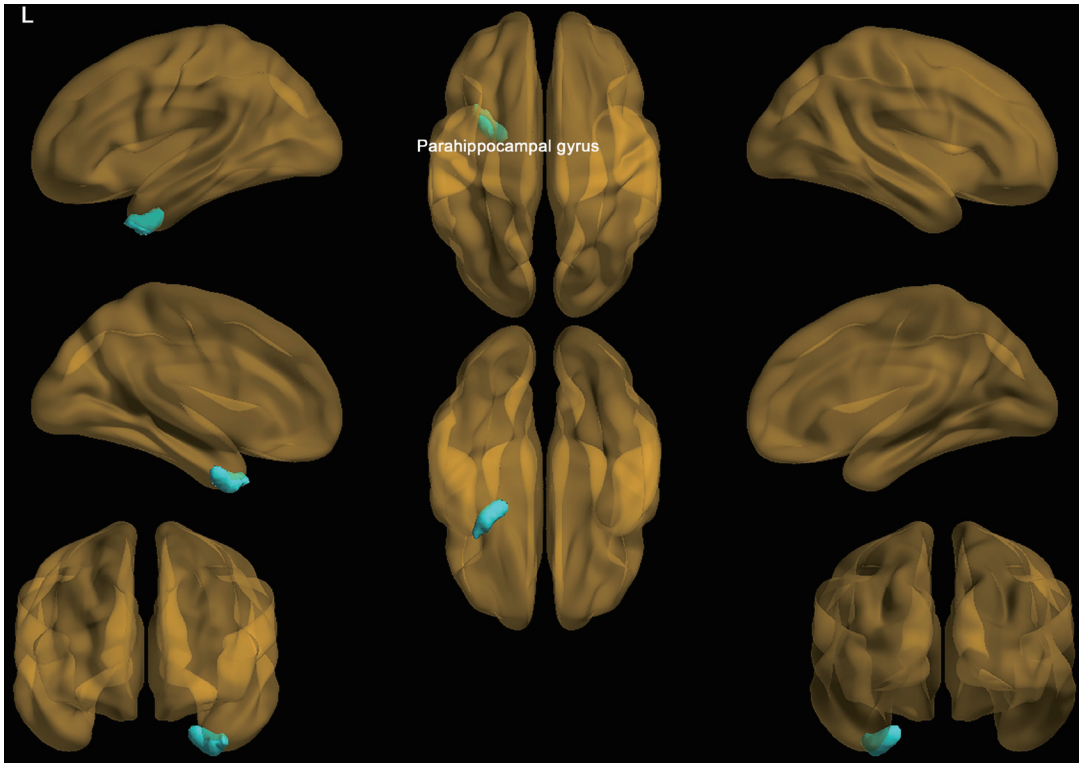

Fig. 4. In the delirium group, the FC between the brainstem ARAS nuclei and the left parahippocampal gyrus is disrupted compared to the non-delirium group. ARAS, ascending reticular activating system; FC, functional connectivity; L, left.

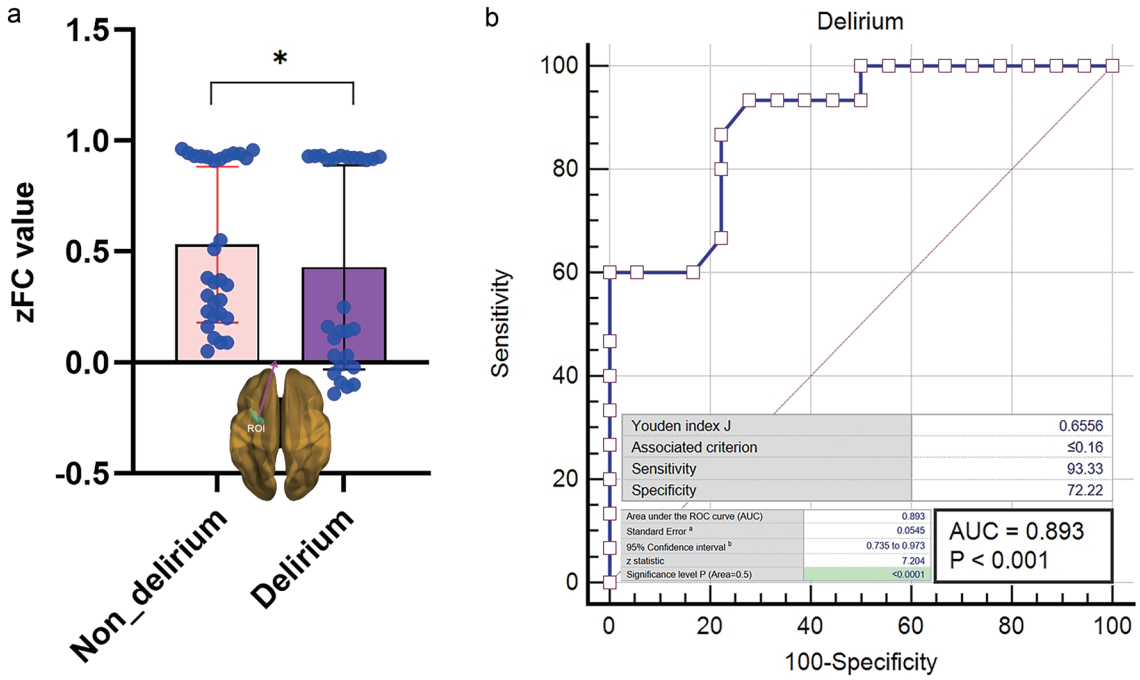

Fig. 5. The parahippocampal gyrus brain region was anchored as the region of interest for further analysis. (a) Compared to non-delirious patients, delirious patients showed significantly reduced zFC values between the brainstem ARAS nuclei and the left parahippocampal gyrus. (b) The zFC values between the brainstem ARAS nuclei and the left parahippocampal gyrus can effectively differentiate patients with delirium from those without delirium after ICH. *p < 0.05. ARAS, ascending reticular activating system; AUC, area under the curve; ICH, intracerebral hemorrhage; ROI, region of interest; zFC, z-score normalization of functional connectivity.

oblongata in the brainstem, which are connected to regions such as the cerebral cortex, limbic system, and basal ganglia through multiple neural pathways.[10] Through these connections, the ARAS is responsible for basic physiological functions such as regulating arousal and controlling sleep cycles, as well as more complex cognitive processes and emotional regulation. When the ARAS functions normally, it coordinates multiple brain regions effectively, ensuring clarity of consciousness and maintenance of alertness.[16] In contrast, any disruption to ARAS function or damage to its core network may lead to symptoms such as arousal disorders, attention deficits, and cognitive disturbances, eventually leading to clinical manifestations such as delirium. Specifically, the brainstem ARAS nuclei primarily communicate with the cerebral cortex, limbic system, and hippocampus through multiple neural projection circuits, particularly via neurotransmitters such as norepinephrine, dopamine, and acetylcholine.[16] These neurotransmitters contribute to ARAS's regulation of arousal and cognitive functions. When these neurotransmitter systems are imbalanced or the projection circuits of the brainstem ARAS nuclei are damaged, the regulation of consciousness and cognitive functions may be interrupted, leading to the onset of delirium.

The left parahippocampal gyrus, as part of the brain's limbic system, is involved of emotional and cognitive functions.[17,18] When the connection between the brainstem ARAS and the left parahippocampal gyrus is disrupted, the function of the parahippocampal gyrus is impaired, resulting in symptoms such as emotional instability, cognitive impairment, and consciousness disturbances. This disconnection may interfere with functions such as emotional regulation, attentional focus, and memory processing, thereby contributing to the development of delirium. The loop between the brainstem ARAS nuclei and the left parahippocampal gyrus may play an essential role in the onset of delirium, and dysfunction in both may be a core mechanism underlying the condition.

The left parahippocampal gyrus is crucial for emotional regulation, memory integration, and cognitive processing.[18] Its normal FC with the ARAS nuclei helps maintain emotional stability and attentional focus. However, when the connection between the brainstem ARAS and the parahippocampal gyrus is disrupted, these functions are weakened, making it easier to experience cognitive confusion, attention deficits, and emotional instability. The enhanced inflammatory response following ICH may exacerbate this process.[19,20] As pro-inflammatory cytokines, such as tumor necrosis factor αand interleukin-1β, are released in the brain, neuronal dysfunction and synaptic transmission are impaired, further affecting the normal release and reception of neurotransmitters, leading to neurochemical imbalance.[21,22] This combination of inflammation and neurotransmitter dysregulation forms the pathological basis for the disruption of FC between the brainstem ARAS nuclei and the left parahippocampal gyrus in patients with delirium. Therefore, restoring normal connectivity between these two regions, regulating inflammatory responses, and balancing the neurotransmitter system may become potential strategies for treating delirium.

For right-handed individuals with ICH, the left hemisphere plays a more dominant role in regulating attention and executive functions. The left hemisphere is traditionally associated with language, logical reasoning, and memory functions, which are crucial in the development of delirium, as it involves integrating sensory and cognitive information essential for maintaining cognitive coherence. Delirium typically presents as an acute confusional state accompanied by fluctuations in consciousness, attention, and speech functions. These symptoms are often exacerbated by disruption of the left hemisphere's language-processing areas and im-

pairment of the left parahippocampal regions that facilitate memory integration. Given the parahippocampal regions' role in memory consolidation, damage to these areas may lead to deficits in short-term memory, spatial orientation, and language-related cognitive functions, all of which are commonly observed in delirium.

Moreover, ROC analysis results show that FC strength (AUC = 0.893) has high predictive ability for delirium and can effectively identify potential delirium patients. This finding suggests that the FC between the brainstem ARAS nuclei and the left parahippocampal gyrus can be used as an effective screening tool for identifying patients at risk of delirium, providing an important basis for early warning. Therefore, as a characteristic fingerprint for predicting delirium occurrence, the FC between the ARAS nuclei and the parahippocampal gyrus provides strong support for clinical diagnosis and treatment strategies.

This study still has some limitations. Although this study demonstrates the potential of FC between the brainstem ARAS nuclei and the left parahippocampal gyrus in predicting delirium, the sample size is relatively small and limited to the basal ganglia ICH population, which may lead to some representational bias. Future research should expand the sample size, consider characteristics of different patient groups, and further validate the universality and stability of the results. This study may not have fully explored changes in FC between the brainstem ARAS nuclei and the parahippocampal gyrus before and after delirium onset. Future research should adopt a longitudinal design to reveal evolving FC patterns at different time points. The study did not investigate the microscopic mechanisms of inflammation and neurotransmitter dysregulation in delirium onset, nor their interactions with brain networks. Future research should integrate molecular biology and brain network science to explore the underlying mechanisms of delirium and identify potential therapeutic targets.

Conclusions

Disruption of FC between the brainstem ARAS nuclei and the left parahippocampal gyrus may underlie the pathogenesis of delirium. The corresponding FC strength could serve as an effective biomarker for predicting delirium onset. Restoring normal connectivity between these regions holds potential as a strategy for early reversal of delirium and represents a key focus for future research.

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Conflict of interest

Jin Hu is an Executive Associate Editor of the journal *Neurosurgical Subspecialties*. The other authors report no conflicts of interest related to this work.

Author contributions

Conception and design (JZ, JH), data collection (JZ, QY, ZYD, MHW, XRY, GW), data analysis (JZ), drafting (JZ), helping with drafting (PFF, QY, MHW, XRY, GW), draft revision (JZ, WJY, JH), and approval of final version (JZ, PFF, QY, WJY, ZYD, MHW, XRY, GW, JH). All authors have approved the final version and publication of the manuscript.

Ethical statement

This study was approved by the Huashan Hospital Ethics Committee Affiliated with Fudan University (20201011 and 2022904). Informed consent was obtained from patients or their families prior to inclusion, and the study was conducted in accordance with the Declaration of Helsinki (as revised in 2024).

Data sharing statement

Data are available from the corresponding author.

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