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Cognitive control subprocess deficits and compensatory modulation mechanisms in patients with frontal lobe injury revealed by EEG markers: a basic study to guide brain stimulation

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ABSTRACT

Background Frontal lobe injury (FLI) is related to cognitive control impairments, but the influences of FLI on the internal subprocesses of cognitive control remain unclear.

Aims We sought to identify specific biomarkers for long-term dysfunction or compensatory modulation in different cognitive control subprocesses.

Methods A retrospective case-control study was conducted. Event-related potentials (ERP), oscillations and functional connectivity were used to analyse electroencephalography (EEG) data from 12 patients with unilateral frontal lobe injury (UFLI), 12 patients with bilateral frontal lobe injury (BFLI) and 26 healthy controls (HCs) during a Go/NoGo task, which included several subprocesses: perceptual processing, anticipatory preparation, conflict monitoring and response decision.

Results Compared with the HC group, N2 (the second negative peak in the averaged ERP waveform) latency, and frontal and parietal oscillations were decreased only in the BFLI group, whereas P3 (the third positive peak in the averaged ERP waveform) amplitudes and sensorimotor oscillations were decreased in both patient groups. The functional connectivity of the four subprocesses was as follows: alpha connections of posterior networks in the BFLI group were lower than in the HC and UFLI groups, and these alpha connections were negatively correlated with neuropsychological tests. Theta connections of the dorsal frontoparietal network in the bilateral hemispheres of the BFLI group were lower than in the HC and UFLI groups, and these connections in the uninjured hemisphere of the UFLI group were higher than in the HC group, which were negatively correlated with behavioural performances. Delta and theta connections of the midfrontal-related networks in the BFLI group were lower than in the HC group. Theta across-network connections in the HC group were higher than in the BFLI group but lower than in the UFLI group.

Conclusions The enhancement of low-frequency connections reflects compensatory mechanisms. In contrast, alpha connections are the opposite, therefore revealing more abnormal neural activity and less compensatory connectivity as the severity of injury increases. The nodes of the above networks may serve as stimulating targets for early treatment to restore corresponding functions. EEG biomarkers can measure neuromodulation effects in heterogeneous patients.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Cognitive control deficits are a key feature of frontal lobe injury (FLI) and involve several separate but related subprocesses. Electroencephalography (EEG) techniques can improve our understanding of how this kind of local damage affects local neural activity and how local changes in brain activity can influence distant but functionally related brain regions. Though non-invasive brain stimulation (NIBS) is emerging as a viable tool to restore both local and widespread brain activity through neuromodulation in patients, a thorough understanding of how the information is processed and transferred to distant regions in specific networks will help us better select stimulating targets and achieve desired benefits.

WHAT THIS STUDY ADDS

⇒ The current study investigated both local and widespread brain activity of different cognitive control subprocesses measured with EEG in individuals with unilateral or bilateral frontal lobe injury (UFLI or BFLI) and healthy control (HC) subjects during a Go/NoGo task. Compared with HCs, the four cognitive control subprocesses of patients with UFLI are either unimpaired or compensatory through the corresponding network connections, whereas patients with BFLI can compensate for the first perceptual processing but not the remaining three subprocesses.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The nodes of the neural network, recruited by cognitive control subprocesses, might serve as a stimulating target of NIBS for early treatment to restore corresponding functions, and such task-based EEG biomarkers could be used as indicators to measure the effect of neuromodulation in specific patients with FLI.

INTRODUCTION

Frontal lobe injury (FLI) is most frequently seen as a consequence of traumatic brain injury (TBI). Damage to the frontal lobes and frontal projections impairs performance

on tasks requiring cognitive control.[1] Cognitive control is necessary, especially when challenged to overcome a habitual movement and select the most appropriate action. Nevertheless, cognitive control involves several separate but related subprocesses, such as perceptual processing, anticipatory preparation, conflict monitoring and response decision, which help to alter or inhibit a prepotent action and act appropriately on task goals or adjust future actions.[2] Although cognitive control has mainly been considered to involve the frontal structures, the effect of FLI on these internal subprocesses of cognitive control remains unclear. Since such higher-level regulatory control and adaptive changes can be detected by Go/NoGo task performance,[3] changes in electroencephalography (EEG), especially the brain network connectivity, linked in patients with FLI during the Go/NoGo task provide an opportunity for us to explore and solve this problem.

EEG techniques have improved our understanding of how local damage affects local neural activity and how local changes in brain activity can influence distant but functionally related brain regions. Re-establishing optimal neural activity is an important component for treating disorders affected by TBI. Non-invasive brain stimulation (NIBS), such as transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS), is emerging as a viable tool to selectively restore both local and widespread brain activity by neuromodulation in patients. However, the clinical efficacy of NIBS is dependent on several factors, including electrode placement, connectedness of the targeted brain region to other regions based on neural networks and whether the participant is concurrently undertaking a task (ie, brain state).[4] When applying NIBS in the clinical domain, we contend that without a thorough understanding of the specific network disturbance of the targeted condition, the desired benefits may not be obtained. Therefore, the study of specific biomarkers of cognitive control subprocesses after FLI helps to quantify the dysfunction objectively, and the reversed changes of biomarkers may reflect the neuromodulation effect. Meanwhile, brain network connectivity helps to understand how the information is processed and transferred to distant but functionally related brain regions during a task, which can also provide ideas for selecting the most effective site for stimulation.

In the search for biomarkers of cognitive control impairment after FLI, prior studies have generally emphasised measures of regional brain function, such as event-related potentials (ERPs) and event-related oscillations (EROs). ERP studies showed that N2 (the second negative peak in the averaged ERP waveform) and P3 (the third positive peak in the averaged ERP waveform) indicated different inhibitory mechanisms, such as the premotor inhibition processes (eg, the detection of conflict) and the inherent inhibitory process (eg, the decision of response). However, for patients with FLI, the pathophysiological deficits of cognitive control subprocesses are controversial. Hughes *et al* and our previous study found that N2 or P3 amplitudes over the central and parietal regions in patients with frontotemporal lesions were diminished compared with healthy subjects.[5 6] In contrast, others indicated that N2 and P3 had no direct differences between patients with FLI and healthy controls (HCs).[7]

For EROs, considering cognitive control subprocesses, the specific role of a brain region governs the functional correlates of oscillations.[2] For example, oscillations over frontal regions reflect inhibitory control, over sensorimotor regions represent motor preparation, and over parietal regions indicate stimulus processing without effects of task demands.[8 9] Similarly, the oscillatory changes in patients with FLI are controversial. Liebrand *et al* found no differences between FLI and healthy subjects in oscillations over frontal, sensorimotor and occipital regions,[8] while others found that patients with FLI showed weaker oscillations over the sensorimotor cortex of a lesioned hemisphere.[10] Therefore, how FLI subtly influences ERPs and EROs in the Go/NoGo task, especially in cognitive control subprocesses, remains unknown.

Furthermore, evidence has documented that distinct cognitive control processes localise to different brain areas and functionally dissociable brain networks. For the functional aspects of cognitive control networks, the dorsal frontoparietal network (DFPN) and the ventral frontoparietal network (VFPN) should be mentioned, as these are related to selecting, maintaining or switching between distinct stimulus–response rules and feature capture, respectively.[11] The functional connectivity between these two networks can guide decision-making by integrating external information with internal representations.[12] In addition, successful resolution of response conflict is accompanied by increased functional connectivity between the midfrontal cortex and the DFPN-related regions (most notably, the dorsolateral prefrontal cortex and the motor cortex).[13] Although network connectivity changes associated with traumatic FLI are not well understood, TBI studies have found that a widespread reduction of functional connectivity is associated with more severe consequences in pathologies and more advanced forms of functional degradation. Moreover, the hyperconnectivity after brain injury has been posited to allocate extra resources to compensate for brain damage.[14] Though functional connectivity may be sensitive to the cognitive sequelae of TBI, the underlying neural network mechanisms of specific cognitive control subprocesses after FLI have not been well elucidated.

In the present study, we investigated multiple biomarkers of long-term dysfunction or compensation of cognitive control subprocesses and the potential brain network mechanisms of neuromodulation in the chronic stage after different types of FLI. EEGs were recorded and measured in patients with either unilateral FLI (UFLI) or bilateral FLI (BFLI) and carefully matched to HC subjects during a Go/NoGo task that included the following cognitive control subprocesses: perceptual processing, anticipatory preparation, conflict monitoring and response decision.[3] We hypothesised that ERPs, EROs or

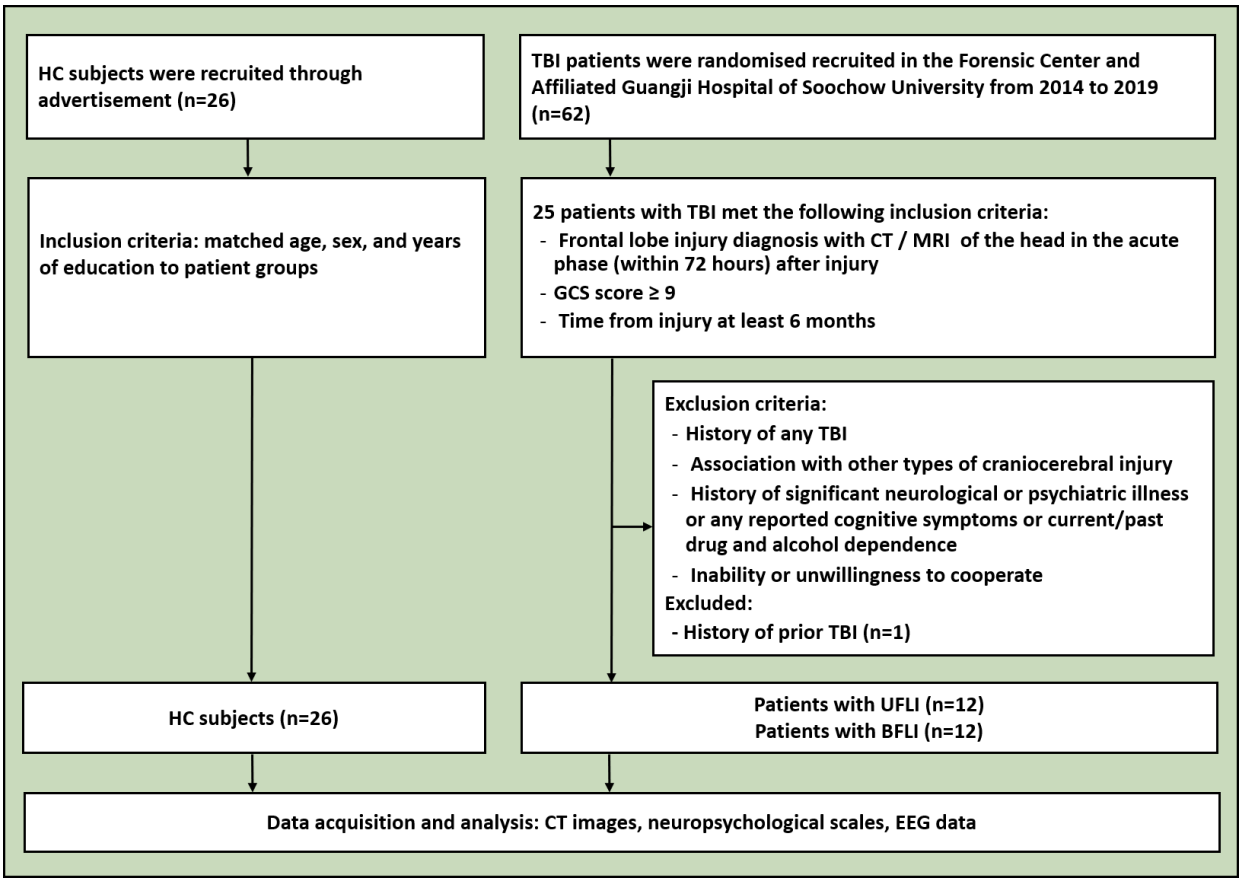

Figure 1 Flowchart of enrolment of the subjects. All of these patients were evaluated by physicians with professional clinical experience based on clinical diagnostic criteria. BFLI, bilateral frontal lobe injury; CT, computed tomography; EEG, electroencephalography; GCS, Glasgow Coma Scale; HC, healthy control; MRI, magnetic resonance imaging; TBI, traumatic brain injury; UFLI, unilateral frontal lobe injury.

functional connectivity could reflect the responses of HCs and different types of FLI on various temporally cognitive control subprocesses, including perceptual processing (parietal oscillations and connectivity of the VFPN), anticipatory preparation (sensorimotor oscillations and connectivity of the DFPN), conflict monitoring (N2 and connectivity of the midfrontal-related networks) and response decision (P3, frontal oscillations and connectivity between the VFPN and the DFPN). Compared with the HCs, the progress of each process in cognitive control after FLI depended on abnormal neural activity and the re-establishment capacity of functional connectivity. We hope that such task-based EEG biomarkers of specific traumatic diseases or neuromodulation can provide pathophysiological bases for the clinical application of NIBS in the treatment of FLI.

METHODS

Participants

The process of participant enrolment is illustrated in figure 1. Traumatic brain injury (TBI) patients were randomized recruited in the Forensic Center and Affiliated Guangji Hospital of Soochow University from 2014 to 2019. Further, two types of FLI patients were diagnosed by physicians with professional clinical experience based on clinical diagnostic criteria, mainly abnormal clinical imaging: frontal lobe contusions or lacerations. Inclusion criteria also included Glasgow Coma Scale (GCS) score ≥ 9 and time from injury at least 6 months. Meanwhile, HC subjects were recruited through advertisement with matched age, sex, and years of education. No subjects had a history of any TBI or association with other types of craniocerebral injury, and history of significant neurological or psychiatric illness or any reported cognitive symptoms or current/past drug and alcohol dependence. As a retrospective case-control study, twelve patients with UFLI (7 left-sided, 5 right-sided), 12 patients with BFLI and 26 HC subjects participated in the following study. All the subjects were right-handed and had the ability and willingness to cooperate. Sample demographic details are summarised in online supplemental table 1.

Experimental design

This study was designed as a retrospective case-control study. All patients underwent computed tomography (CT) scans in the acute stage; a second CT scan was also performed in the chronic stage (>6 months after injury). Meanwhile, neuropsychological tests and EEG recordings were carried out on patients only at the chronic stage;

they were also conducted on the control subjects for normative data and comparison with patients.

CT morphological measurement

The lesion volumes were calculated individually using ImageJ (V.1.53). Brain CT images were opened in ImageJ, and the lesions were outlined on each slice using an established density threshold. The different lesion areas were automatically added slice by slice and then multiplied by the slice thickness to obtain a final individual volume for each patient.

Neuropsychological assessment

Neuropsychological tests included the (1) Mini-Mental State Examination (MMSE) measuring global cognition[15]; (2) digit-span forward and backward, assessing attention and working memory[15]; (3) digit symbol to assess processing speed[6]; and (4) block design to measure visuospatial attention and motor skills.[6]

Electrophysiological measurement

Task

The visual Go/NoGo task comprised 180 Go trials (double triangles) and 120 NoGo trials (single triangle), split into three equal blocks. Each trial started with an instantaneous white fixation cross presented centrally on a dark background, followed by the Go or NoGo stimuli. The stimulus presentation time was 50 ms, and the interstimulus interval was set at 800 ms. Participants were asked to press a key with the right index finger for the Go condition and refrain from pressing for the NoGo condition. Before the EEG recording, all participants were given 16 practice trials and confirmed that they had understood the task. Reaction time (RT), accuracy rate (ACC) of the Go condition and error rate of the NoGo condition were recorded during the test section.

EEG data acquisition

With a Neurolab Neuro40 Amplifier (www.neurolab.com.cn), EEGs were recorded continuously from a NeuroCap with 32-channel Ag/AgCl electrodes according to the expanded international 10-20 system. EEG data were recorded across 1000 Hz (0.1 Hz high-pass and 200 Hz low-pass online filters), and electrode impedances were required to be below 5 kΩ. Two electrodes for the horizontal electrooculograms (EOGs) were placed at the outer canthi of both eyes. Two electrodes for the vertical EOGs were placed above and below the left eye. EEG data were referenced to the nasal root with a ground channel at frontal pole zone (FPZ). For patients with lesions in the right hemisphere (n=5), electrodes in the right hemisphere were exchanged before offline analyses so that left hemisphere electrodes were synonymous with the lesioned hemisphere for further analyses and illustrations.

Time-domain and time-frequency analyses

Offline data for time-domain and time-frequency features were analysed using EMSE V.5.6 software. EEG data were re-referenced to the common average reference. Artefacts related to saccades or eyeblinks were first empirically identified using visual inspection. Next, a built-in spatial filter software was applied for ocular artefact correction that could remove eye movement and blink artefacts without removing the frontal-generated data.

EEG signals were filtered with a low-pass filter at 30 Hz (24 dB/octave) for time-domain analyses. Then, the segmentation of EEG data was performed into epochs from 200 ms pre-stimulus to 800 ms post-stimulus. A baseline correction was implemented on EEG data based on the 200 ms pre-stimulus period. Any epoch with an amplitude exceeding ±100 µV at any electrode was rejected before averaging. According to the grand-averaged waveforms, peak latency and mean amplitude of Go-N2 (150–240 ms), Go-P3 (240–390 ms), NoGo-N2 (180–300 ms) and NoGo-P3 (300–430 ms) were measured for each subject. Given our results and associated studies,[6] central–parietal regions (C3/Z/4, CP3/Z/4, P3/Z/4) were analysed under Go conditions, while frontal–central regions (F3/Z/4, FC3/Z/4, C3/Z/4) were analysed under NoGo conditions.

For time-frequency analyses, EEG signals were segmented into epochs from 300 ms pre-stimulus to 800 ms post-stimulus without using the filter. Then, baseline correction and artefact rejection processes were conducted. The time series of EEG signals were transformed into time-frequency signals using the wavelet transform algorithm. Power was calculated from the result of the complex convolution for each trial. Frequencies >30 Hz were not studied since these are particularly affected by muscle artefacts, eye movements and microsaccades. According to the grand-averaged spectrum, time-frequency windows of interest were defined as follows: 150–550 ms after stimulus presentation to analyse EROs for delta (1–4 Hz), theta (4–8 Hz), alpha (8–13 Hz) and beta (13–30 Hz) frequency bands. Based on previous studies[16] and our topographical plots, frontal regions (F3/Z/4), central sensorimotor regions (C3/Z/4) and parietal regions (P3/Z/4) were selected for further analysis.

Functional connectivity analysis

All data processing and analysis were performed using custom scripts and the EEGLAB Toolbox in MATLAB V.R2019a. Continuous EEG data were downsampled to 500 Hz and re-referenced offline to the average reference. All electrodes were band-pass filtered between 0.1 and 100 Hz and notch-filtered at 50 Hz. Then, trials were divided into 1100 ms segments, including a 300 ms pre-stimulus baseline period. Epochs were rejected if the absolute voltage of any electrode exceeded 100 µV. Epochs contaminated by eyeblinks and movements were corrected using an independent component analysis (ICA) algorithm. Then, the current source density, the Laplacian of scalp surface voltage, was used to eliminate volume-conducted contributions from distant regions and sources.

Functional connectivity was estimated using the weighted-phase lag index (WPLI), a measure of phase synchronisation less affected by volume conduction and

reference montage by accounting for only non-zero phase lead/lag relationships. Four frequency bands of interest were consistent with the time-frequency analyses. First, for each frequency band, we compared baseline WPLI and post-stimulus WPLI in each group to determine task-related changes in functional connectivity. Then, Z transformation was performed on the WPLI: the post-stimulus WPLI minus the mean of the baseline WPLI and then divided by the standard deviation (SD) of the baseline WPLI to obtain the standardised WPLI (SWPLI). Given the grand-averaged whole-brain connectivity plots, we determined time windows for each frequency band, that is, post-stimulus 100–500 ms for the delta band, 0–500 ms for the theta band, 0–400 ms for the alpha band and 0–300 ms for the beta band. Therefore, whole-brain connectivity was calculated by averaging the SWPLI matrix during the time windows.

All electrodes were grouped into prefrontal, frontal, parietal or occipital regions to evaluate the functional connectivity between brain regions. The frontal and parietal regions were further divided into the middle, dorsal and ventral regions (online supplemental figure 1). Significant functional connections were also classified into five larger categories: posterior, ventral frontoparietal, dorsal frontoparietal, midfrontal-related and interfrontoparietal network connectivity. Functional connectivity difference maps were visualised using BrainNet Viewer.

Statistical analyses

All statistical analyses were performed by SPSS V.20; $p<0.05$ was considered significant.

The lesion volumes were analyzed by one-way analysis of variance (ANOVA) with the group UFLI vs BFLI in the specific period of brain injury. Besides, the lesion volumes were also analyzed by one-way ANOVA with the period of brain injury (acute stage vs chronic stage) in the specific patient groups. The neuropsychological scales and behavioural performances were carried out by one-way ANOVA with the group HC vs UFLI vs BFLI. For ERPs, the peak latencies and mean amplitudes of each ERP component were analyzed by a three-way repeated-measure ANOVA with the group HC vs UFLI vs BFLI as the between-subject factor, while regions and laterality (left vs midline vs right) as the within-subject factors. For EROs, the power of the frontal, sensorimotor and parietal oscillations was submitted to a two-way repeated-measure ANOVA with the group HC vs UFLI vs BFLI as the between-subject factor, and laterality (left vs midline vs right) as the within-subject factor. For functional connectivity, intragroup characteristics of each group were analysed using a paired t-test (two-tailed) to compare the baseline WPLI and post-stimulus WPLI in each group. Then, the comparison of the averaged SWPLI between groups for each band was determined by one-way ANOVA with the group HC vs UFLI vs BFLI.

Greenhouse-Geisser corrections were made when appropriate. Bonferroni corrections were used to correct for multiple comparisons. Tukey Honestly Significant Difference (HSD) tests were conducted as post hoc analyses. Post hoc power analysis for various statistical tests was performed using G*Power V.3.1.9.7, and only the results with statistical power over sufficient limits (80%) were statistically effective.

Correlation analyses

A partial correlation between two variables is defined as the correlation of two variables while controlling for a third or more variables. The partial correlation coefficient is said to be adjusted or corrected for the influence of the different covariates. To quantify the current clinical outcomes of FLI, after controlling the confounding factors of the group,[6] partial correlation analyses were used to compare the relationships between neuropsychological tests/behavioural performance (Go reaction times, Go accuracy rate or NoGo error rate) and the above-mentioned significant EEG measures (the mean values among the regions of interest).

RESULTS

CT morphological measurements, neuropsychological assessments and behavioural results all showed significant differences between HCs and patients, while no differences were observed between the UFLI and BFLI groups. Details are shown in online supplemental results and online supplemental tables 1 and 2.

Event-related potential results

The grand-averaged waveforms and topographies of ERP under the Go and NoGo conditions are shown in figure 2. For N2, only the peak latencies for Go-N2 in the BFLI group were longer than in the HC group. For P3, the mean amplitudes for Go-P3 and NoGo-P3 in the HC group were larger than in the UFLI and BFLI groups. Details are shown in online supplemental results and online supplemental tables 3 and 4.

Event-related oscillation results

The time-frequency plots and topographies of oscillations under the Go and NoGo conditions are shown in figure 3, and significant differences were found in the delta and theta bands (online supplemental figures 2–4). The frontal and parietal oscillations were higher in the HC group than in the BFLI group under the Go condition, while they were higher in the HC group than in the UFLI and BFLI groups under the NoGo conditions. The sensorimotor oscillations in the HC group were higher than in the UFLI and BFLI groups under both the Go and NoGo conditions. Details are shown in online supplemental results and online supplemental table 5.

Functional connectivity results

Global properties of functional connectivity

Figure 4A,B illustrates the whole-brain functional connectivity of the HC, UFLI and BFLI groups; significant group effects were observed as seen in figure 4C (see online supplemental results for details).

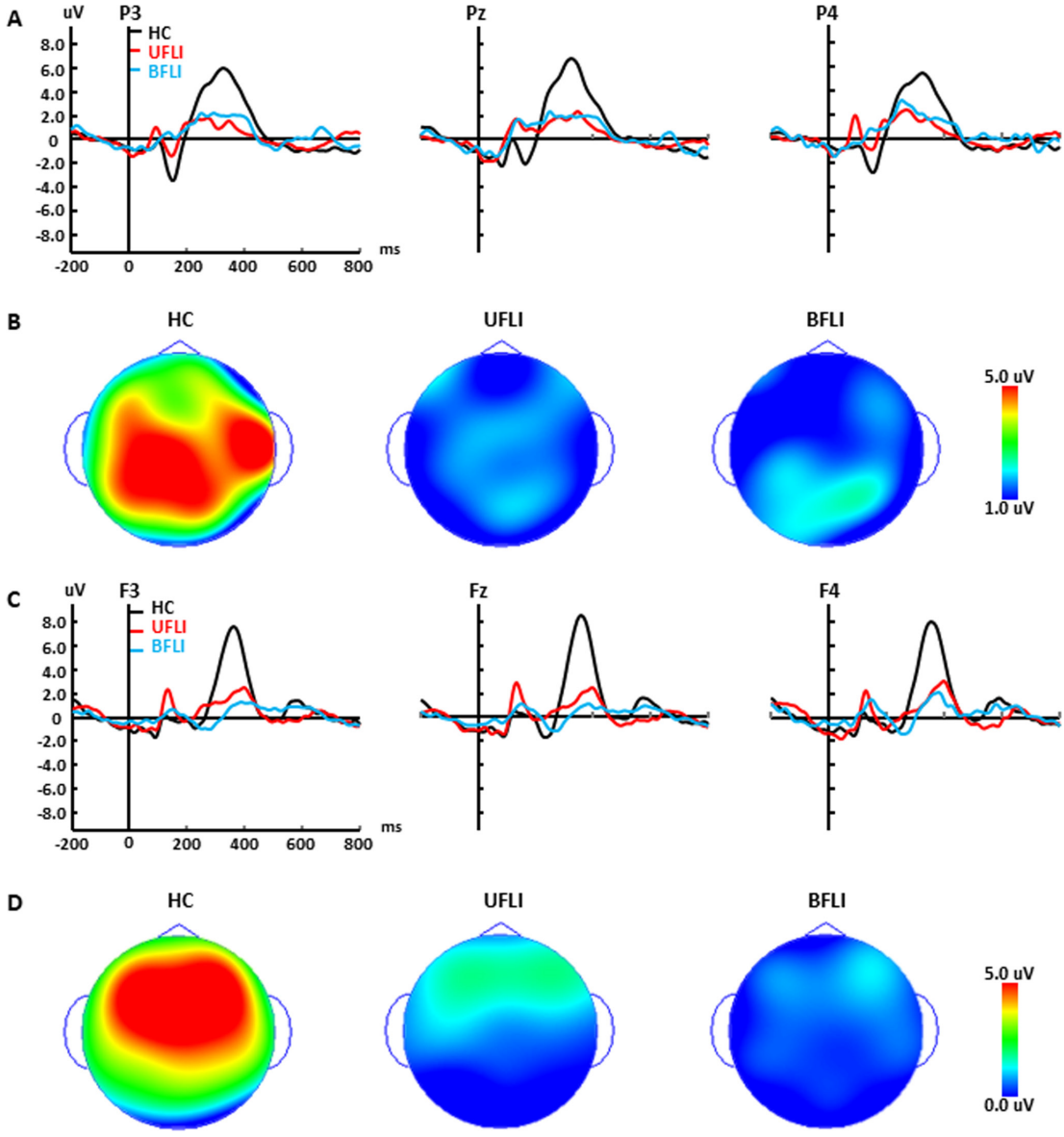

Figure 2 Event-related potential results under Go and NoGo conditions. (A) Average ERP waveforms for HC, UFLI and BFLI groups under the Go condition. Black line: responses of HCs. Red line: responses of patients with UFLI. Light blue line: responses of patients with BFLI. The representative electrode locations are as follows: left parietal (P3), middle parietal (Pz) and right parietal (P4) scalp sites. (B) Topographical maps of the P3 (240–390 ms) for the HC, UFLI and BFLI groups under the Go condition. (C) Average ERP waveforms for the HC, UFLI and BFLI groups under the NoGo condition. Black line: responses of the HCs. Red line: responses of patients with UFLI. Light blue line: responses of patients with BFLI. The representative electrode locations are as follows: left frontal (F3), middle frontal (Fz) and right frontal (F4) scalp sites. (D) Topographical maps of the P3 (300–430 ms) for HC, UFLI and BFLI groups under the NoGo condition. BFLI, bilateral frontal lobe injury; ERP, event-related potential; HC, healthy control; UFLI, unilateral frontal lobe injury.

Regional properties of functional connectivity

The results of the within-group comparisons are described in the online supplemental results and online supplemental figure 5. Details are shown in online supplemental tables 6–11.

The results of the comparison between groups are shown in figure 5, along with the mean adjacency matrices and group differences in functional connectivity under the Go and NoGo conditions (online supplemental figure 6). For the VFPN, there were no significant group effects for almost all functional connections. For the posterior brain networks, the connections were significantly lower in the BFLI group than in the HC and UFLI groups under the Go and NoGo conditions. For the DFPN, the delta and theta connections in the bilateral hemispheres of the BFLI group were significantly lower than in the HC and UFLI groups under the Go and NoGo conditions. In contrast, compared with the HC group, the UFLI group showed increased theta connections in the uninjured hemisphere and a series of alpha connection enhancements in the injured hemisphere only under

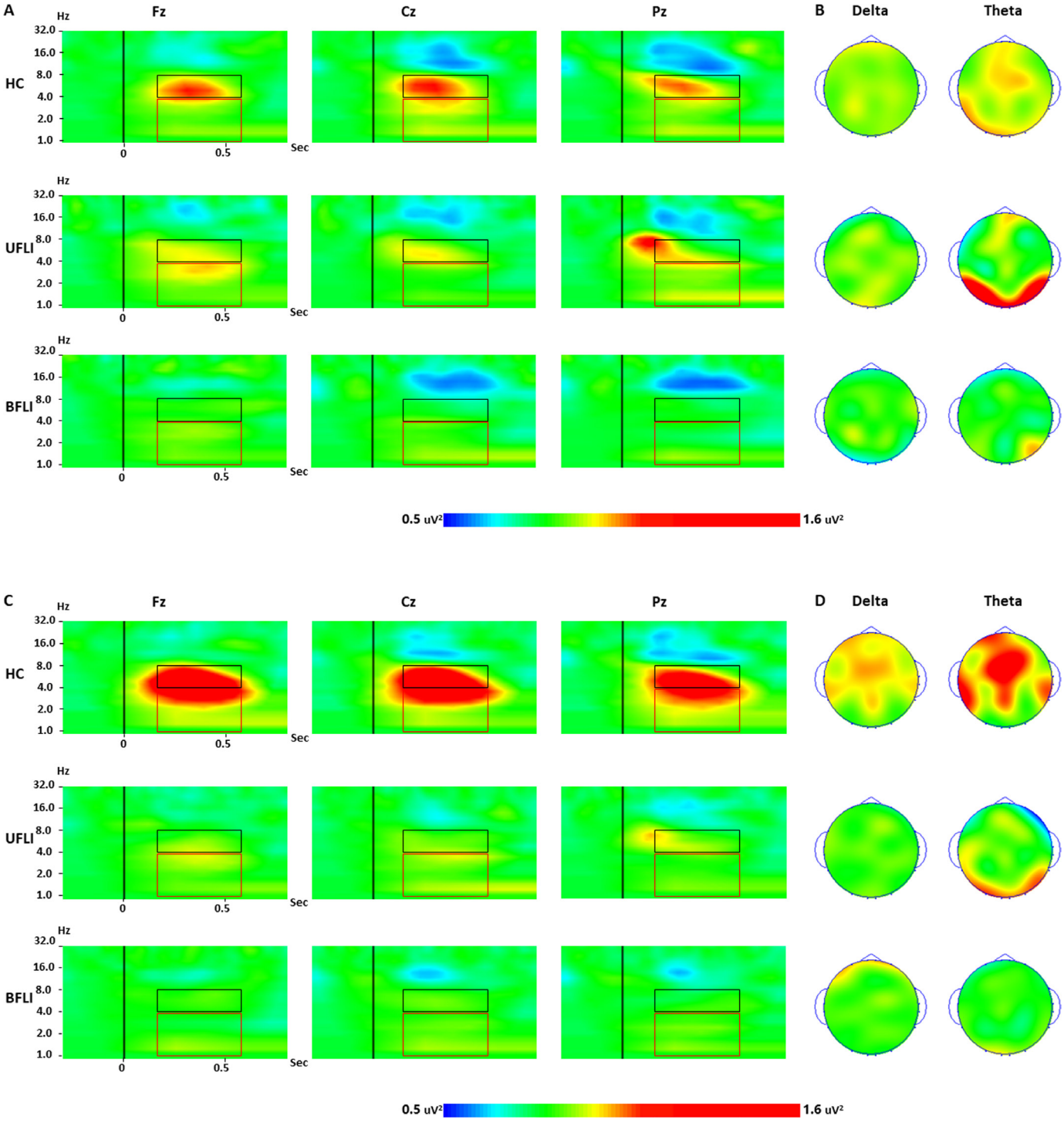

Figure 3 Event-related oscillation results under Go and NoGo conditions. (A) Time-frequency spectrograms of Go oscillatory power are plotted separately for HC (top panel), UFLI (median panel), and BFLI (bottom panel) groups at the middle frontal (Fz), middle central (Cz) and middle parietal (Pz) scalp sites. The red and black solid boxes indicate the delta (1–4 Hz) and theta (4–8 Hz) frequency bands in the same time window (150–550 ms) of interest, respectively, that are averaged for the analysis of variance (ANOVA). (B) Topographical maps of delta (left panel) and theta (right panel) power are plotted separately for HC (top panel), UFLI (median panel), and BFLI (bottom panel) groups averaged across all trials within Go blocks. (C) Time-frequency spectrograms of NoGo oscillatory power are plotted separately for HC (top panel), UFLI (median panel) and BFLI (bottom panel) groups at the middle frontal (Fz), middle central (Cz) and middle parietal (Pz) scalp sites. The red and black solid boxes indicate the delta (1–4 Hz) and theta (4–8 Hz) frequency bands in the same time window (150–550 ms) of interest, respectively, that are averaged for the ANOVA. (D) Topographical maps of delta (left panel) and theta (right panel) power are plotted separately for HC (top panel), UFLI (median panel) and BFLI (bottom panel) groups averaged across all trials within NoGo blocks. BFLI, bilateral frontal lobe injury; HC, healthy control; UFLI, unilateral frontal lobe injury.

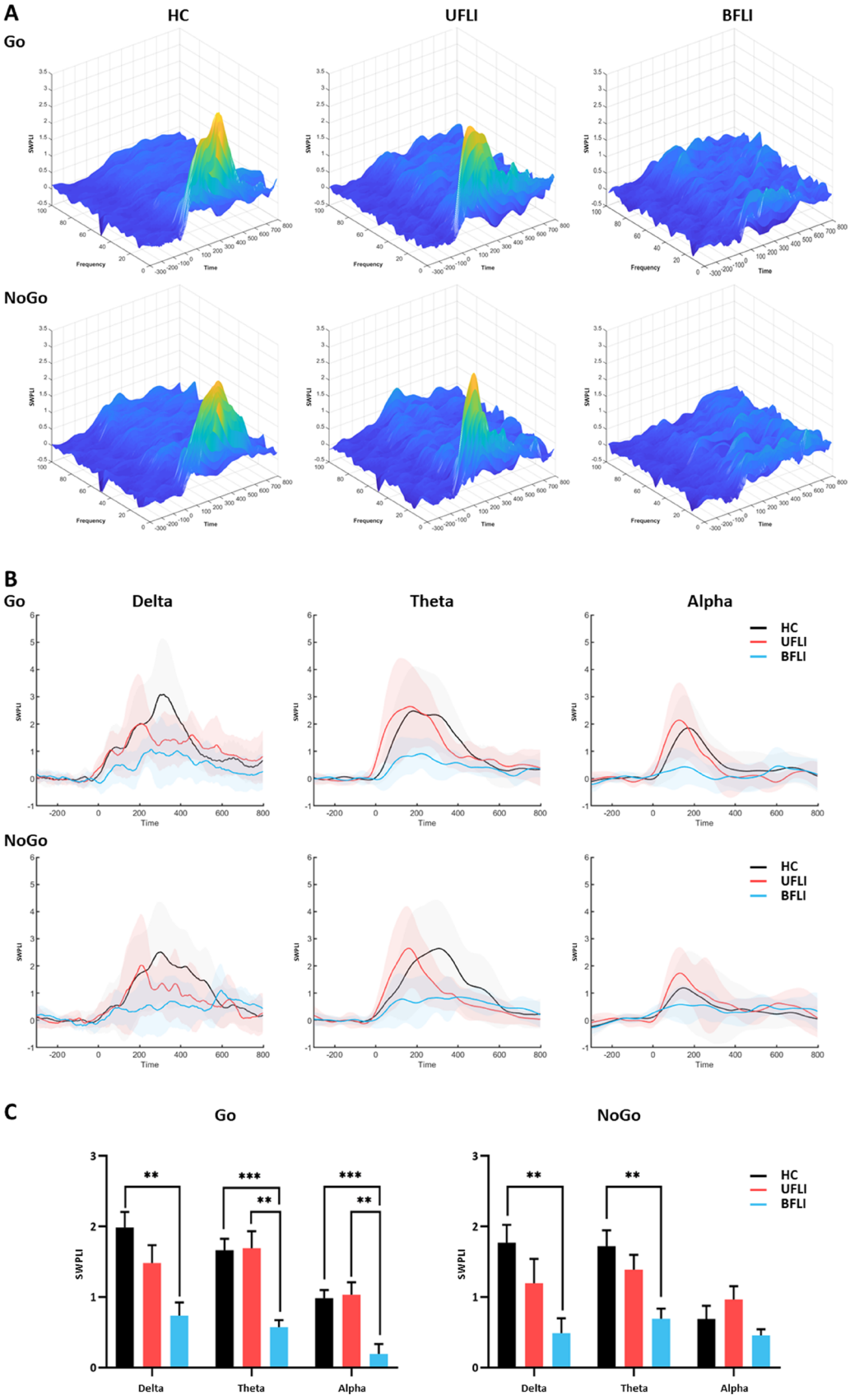

Figure 4 Global functional connectivity under Go and NoGo conditions. (A) Average SWPLI at 0.1~100 Hz from −300 ms to 800 ms after the stimuli in the HC, UFLI and BFLI groups. (B) Time courses of the average SWPLI for delta, theta and alpha frequency bands in HC, UFLI and BFLI groups. (C) Statistical results of the whole-brain SWPLI for delta, theta and alpha frequency bands. **p<0.01, ***p<0.001. BFLI, bilateral frontal lobe injury; HC, healthy control; SWPLI, standardised weighted-phase lag index; UFLI, unilateral frontal lobe injury.

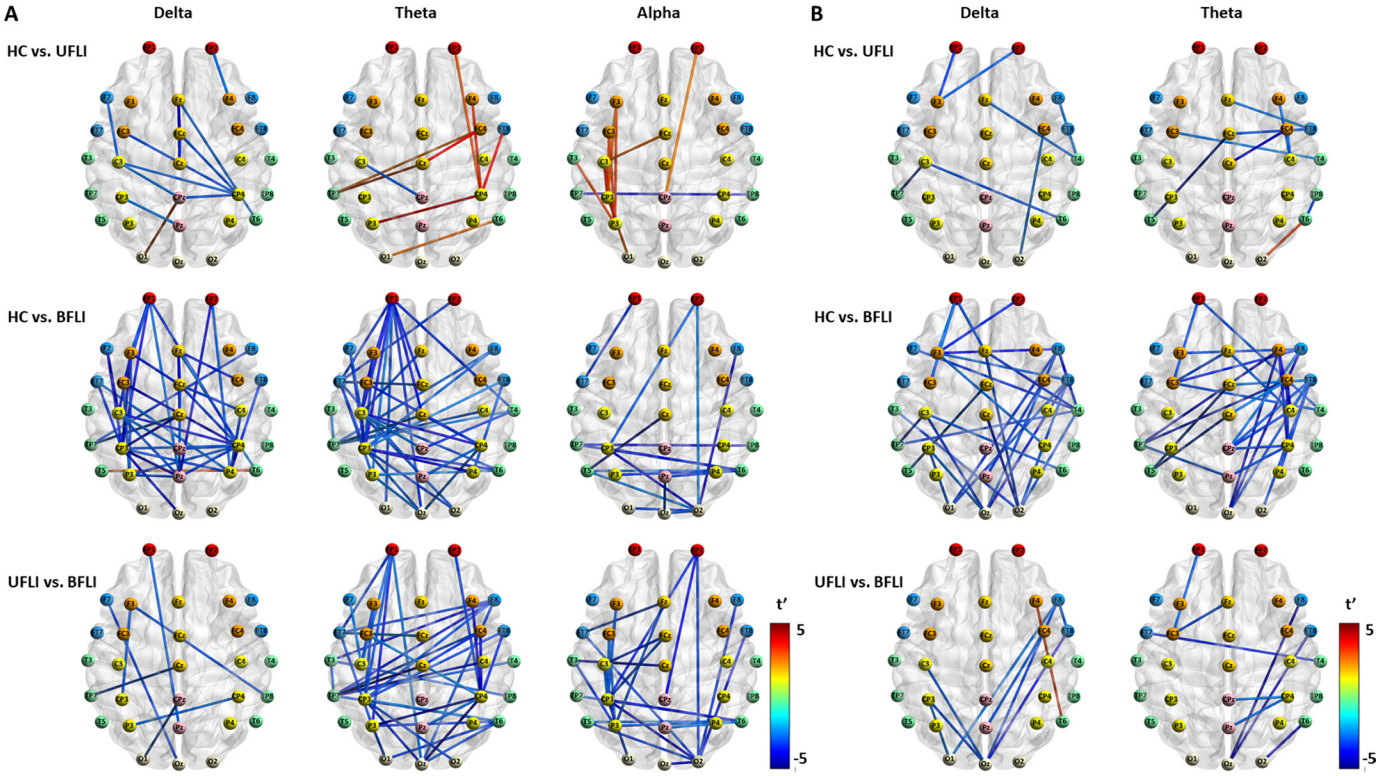

Figure 5 Topographical differentiation between groups for functional connectivity under Go and NoGo conditions. (A) Significant topographical representations between channels for delta, theta and alpha frequency bands of the HC group versus the UFLI group, the HC group versus the BFLI group, and the UFLI group versus the BFLI group under the Go condition. The red colour indicates higher values for the second group than the first group, the blue colour indicates the opposite. (B) Significant topographical representations between channels for delta and theta frequency bands of the HC group versus the UFLI group, the HC group versus the BFLI group, and the UFLI group versus the BFLI group in the NoGo condition. The red colour indicates higher values for the second group than the first group, the blue colour indicates the opposite. BFLI, bilateral frontal lobe injury; HC, healthy control; UFLI, unilateral frontal lobe injury.

the Go condition. Compared with the HC group, the midfrontal-related brain networks of the BFLI group showed diminished delta and theta connections under the Go and NoGo conditions but almost none in the UFLI group. For functional connectivity between the DFPN and the VFPN, compared with the HC group, the BFLI group showed decreased delta and theta connections under the Go and NoGo conditions. In contrast, the UFLI group showed increased theta connections under the Go condition but not in the NoGo condition. Details are shown in online supplemental results and online supplemental tables 12–15.

Correlation analyses

Statistically significant correlations between neuropsychological tests/behavioural performance and functional connectivity were observed under the Go condition (online supplemental figure 7). For the posterior brain networks, the alpha connectivity was negatively correlated with MMSE scores (r=−0.426, p=0.043) and digit-span backward (r=−0.466, p=0.025). For the DFPN, the theta connectivity in the right hemisphere was negatively correlated with the RTs (r=−0.490, p=0.018).

DISCUSSION

Main findings

To guide the clinical application of NIBS, we identified the neural indices (ERPs, EROs and functional connectivity) of cognitive control impairments. We also assessed the natural neuromodulation mechanisms of patients with FLI in a Go/NoGo task. We discussed specific EEG markers according to the four subprocesses of cognitive control to explore which part was impaired and whether the corresponding compensatory modulation mechanisms were initiated. The first subprocess encompassed vigilance/alerting (the parietal oscillations and connectivity of the posterior brain networks) and general stimulus processing (connectivity of VFPN), both of them were not impaired or recovered by natural compensatory mechanisms in patients without exogenous neuromodulation. The second subprocess involved anticipatory preparation (sensorimotor oscillations and connectivity of DFPN), which was impaired in patients with BFLI but was preserved in patients with UFLI. Here, the connectivity indicators suggested that stimulating the brain regions involved in the DFPN through NIBS can mobilise neuromodulation and alleviate abnormal behaviours to some extent. The third subprocess represented conflict

monitoring (N2 and connectivity of the midfrontal-related brain networks), which was impaired only in patients with BFLI, so activation of this network by stimulating the medial frontal cortex might yield reliable neuromodulation effects. The fourth subprocess was response decision (P3, frontal oscillations and the connectivity between the VFPN and the DFPN), which was impaired in patients with BFLI but was partially preserved in patients with UFLI; it provided neural network-based evidence in searching for stimulating targets for NIBS as well as biomarkers of neuromodulation.

Comparison of perceptual processing

First, the exogenous visual stimulus has to be perceived. The ability to sustain attention (ie, vigilance/alerting), a vital component of visual perception, was related to neural activity in the parietal brain region,[9] and the abnormal neural oscillations involving the posterior region could reflect individuals at high risk of cognitive disturbance.[17] Therefore, our results of parietal oscillations suggest that patients with BFLI have a high risk of cognitive disturbance, including defects in allocating attention to inhibit irrelevant information and in maintaining sustained attention.

To compensate for the defects of attentional allocation, the alpha functional connections in the posterior brain regions (parietal-occipital) that contribute to maintaining alertness were activated, and they were negatively related to the alerting effect.[18] The hypoconnectivity in patients with BFLI meant that they more severely needed to mobilise compensatory connectivity to increase alertness. Moreover, the hypoconnectivity in the alpha band was associated with higher scores of the MMSE and digit-span backward test, confirming that it could be a compensatory mechanism for global cognition, attention or even working memory. The existence of compensatory connections might rely on dopamine and dopamine transporters, which regulate attentional alerting by modulating neuronal activity in the posterior parietal cortex.[19]

Another component of visual perception was general stimulus processing, accompanied by a neural marker (VFPN) that was generally involved in the bottom-up capture of feature representations.[11] No group differences were found, verifying the stability of bottom-up input through over-recruitment of cognitive resources in the chronic stage of TBI.[20] However, this excessive dissipation of the limited cognitive resources resulted in a progressive decrease in the resources available to complete subsequent task processing.

Comparison of anticipatory preparation

After perceiving the stimulus, an anticipatory preparation has to be made for forthcoming stimuli and actions. Altered activity over the sensorimotor cortex was related to motor preparation and anticipatory attention, reflected in beta and theta bands, respectively.[21 22] Our results were consistent with a previous FLI study showing no group differences for sensorimotor beta oscillations.[8] However, sensorimotor theta oscillations in patients with UFLI and BFLI were lower than in HCs, reflecting deficits of anticipatory attention in these patients.

Further, we analysed the theta functional connections in the DFPN because the DFPN was recruited to control top-down sources of attentional capture.[11] Compared with HCs and patients with UFLI, these functional connections were decreased in patients with BFLI, verifying that specific abnormalities in the DFPN reflected the severity of deficits in maintaining and manipulating information in goal-directed attention. These decreases further proved there were fewer residual cognitive resources for anticipatory attention in patients with BFLI after the overconsumption in the previous process. These phenomena could be explained as rotational shearing of white matter tracts, exhibiting the TBI-induced impairments in the generation, maintenance and precise timing of anticipatory neural activity.[23] In contrast, these theta functional connections were increased in the uninjured hemisphere of patients with UFLI relative to HCs, which possibly acted as a compensatory mechanism during the post-traumatic recovery stage. This assumption was proved by our correlation results that better behavioural performances were associated with greater levels of these theta connections. Meanwhile, the increased alpha connections within the DFPN occurred in the injured hemisphere of patients with UFLI relative to HCs, which might represent an excitation/inhibition balance dysfunction.[24] All these findings suggested that this top-down process was decompensated in patients with BFLI, but was compensated for in patients with UFLI by the DFPN in the uninjured hemispheres, indicating the nodes of the DFPN might be used as network targets for the neuromodulation after FLI. NIBS acts on the nodes of the DFPN, such as the dorsolateral prefrontal cortex or posterior parietal cortex, and has been used to treat cognitive impairment after TBI,[25 26] and increased activation within the DFPN was proposed in a case report.[27] Therefore, our research could provide reliable biomarkers for a possible therapeutic effect of BFLI and a new idea that early neuromodulation of NIBS might be achieved in patients with BFLI by establishing the above compensatory connections.

Comparison of conflict monitoring

Response conflict must be monitored when two incompatible response tendencies are simultaneously active. On the one hand, Go/NoGo-N2 represented response conflict monitoring on correct trials. Our Go-N2 results demonstrated patients with BFLI had longer peak latencies than HCs. Previous studies found that patients with TBI exhibited lower amplitudes and longer latencies, but while in rehabilitation, they exhibited larger amplitudes and shorter latencies.[28] Thus, patients with BFLI with abnormal latencies exhibited a delayed process in conflict monitoring.

On the other hand, the theta functional connections between the midfrontal cortex and the dorsal frontal/parietal regions were positively related to the detection of

response conflict.[13] The hypoconnectivity of this network in patients with BFLI meant that the conflict monitoring of patients with BFLI was abnormal and ineffective, and they had trouble assessing the need for cognitive control to elevate the decision threshold and prevent impulsive responses. The intrinsic mechanism might be reductions in oxyhaemoglobin concentration levels and cerebral blood flow during the conflict processing in patients with TBI.[29] Conflict monitoring was only impaired in patients with BFLI, confirming that conflict monitoring depended on the integrity of cognitive function, and decompensation of the above processes led to the cascade changes of cognitive control dysfunction. It was reported that tDCS targeting the frontal midline electrodes increased activities of the midfrontal-related brain networks in individuals with chronic TBI,[30] implying this approach might be used to improve abnormal conflict monitoring in patients with BFLI.

Comparison of response decision

After the above processes, a decision must be made whether or not to transform into a motor operation. In this process, Go-P3 represented a strategic process of contextual updating, whereas NoGo-P3 reflected an inhibitory control process of replacing the prepared response with an alternative response. Here, results were consistent with our previous study,[6] and patients with UFLI or BFLI had difficulty updating the context and withholding the prepared response.

In addition, frontal theta oscillations are important during the strategic planning of actions in response to a stimulus.[16] This function was disrupted only in patients with BFLI due to the decreased frontal theta activity in the Go condition. However, in the NoGo condition, the delta and theta frontal oscillations decreased in patients with either UFLI or BFLI, reflecting the failure of response inhibition and likely reaching the ceiling activity.[30]

Furthermore, we discussed functional connectivity between the DFPN and the VFPN that could guide decision-making by integrating external information with internal representations.[12] In a Go condition, the internetwork hypoconnectivity in patients with BFLI, especially prefrontal-related desynchronisation, represented defects in integrating functions. Likewise, the stimulation of densely connected neural hubs, such as the prefrontal region, could cause widespread changes, including reversed long-range desynchronised connectivity, in patterns of integration across brain areas and systems.[4] This might help the neuromodulation of patients with BFLI, and the neural network targets might be FP1/2 electrodes in this brain state. Conversely, the internetwork hyperconnectivity in patients with UFLI reflected the compensatory mechanism contributing to faster processing speed to promote the capability of response decisions. However, our correlation analysis did not find any correlations between behavioural performances and internetwork connectivity, possibly due to the small sample size; thus, this needs to be further verified by future research. The VFPN also has been considered a circuit breaker for the DFPN, which controls the current focus away from the continuous item.[11] In a NoGo condition, the internetwork hypoconnectivity in patients with UFLI or BFLI implies the failure of the circuit breaker would lead to a further reduction in response inhibition.

Limitations

This study had some limitations. First, the study was confined to a small sample size due to recent difficulties in collecting data from clinical patients. Thus, reported results should be further investigated in larger samples. Second, we performed only a 6-month follow-up due to the limitations imposed by the coronavirus disease 2019 (COVID-19) epidemic prevention and control measures. Longer-term outcomes will be recorded and reported in future work. Furthermore, our future EEG studies will be combined with multimodalities of NIBS, such as TMS and tDCS, among patients with FLI to prove the therapeutic effect of relevant stimulating targets.

Implications

As the severity of TBI increased, the top-down system became more degraded, and the modulation became slower than that of the bottom-up system, therefore the former might be more sensitive to NIBS intervention. Patients with UFLI had no processing deficits in the first bottom-up process, and patients with BFLI also maintained relatively intact bottom-up perceptual processing due to the compensation of the alpha connectivity between the posterior brain regions. Subsequently, in the following three top-down processes, patients with UFLI had unimpaired conflict monitoring, and recovered their anticipatory preparation through the compensatory connectivity of the DFPN in the uninjured hemisphere and their response decision through the compensatory connectivity between the DFPN and the VFPN. Nevertheless, patients with BFLI progressed to long-term dysfunction, presenting multiple abnormalities in EEG measures without corresponding compensatory manifestations.

On the one hand, the nodes of the above neural network—the dorsolateral prefrontal cortex or the posterior parietal cortex in the DFPN, the medial frontal cortex in the midfrontal-related brain networks and the prefrontal region (frontopolar) in across-networks—might serve as stimulating targets of NIBS for early treatment restoration of corresponding functions. On the other hand, EEG biomarkers, especially the reconstruction of the above-mentioned compensatory connectivity, could be used as indicators to measure the effects of neuromodulation. Our findings have important implications for EEG-based clinical diagnosis in the chronic stage of TBI and provide a latent neuromodulation therapeutic strategy for patients with FLI.

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Ethics approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee. The study was approved by the Ethics Committee of Soochow University (reference number: SZUM2008031233), and informed consent before participation was obtained from each subject according to the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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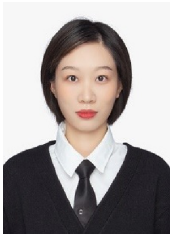

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