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Original Research

Differences in Cognitive Impairment and Functional Plasticity Between Asymptomatic Cerebral Arterial Stenosis and Asymptomatic Intracranial Atherosclerotic Stenosis: An Event-Related Potential Study

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Abstract

Background: Asymptomatic carotid stenosis (ACS) and asymptomatic intracranial atherosclerotic stenosis (aICAS) present ongoing treatment challenges. These conditions can lead to cognitive impairment through cerebral hypoperfusion and silent cerebral embolism. However, it is unclear whether they result in the same degree of cognitive dysfunction. Furthermore, the neurological mechanisms behind these dysfunctions are still not well understood. This study used cognitive neuro-electrophysiological techniques to examine differences in cognitive impairment caused by ACS and aICAS. **Methods**: A total of 22 patients with ACS and 15 patients with aICAS were enrolled, all with at least 70% unilateral severe stenosis. The control group (CG) consisted of 23 patients who were matched with the ACS and aICAS groups for age, gender and vascular risk factors. All participants conducted the flanker task, and their behavioral and neuroelectric data were also collected. Cognitive impairment of the hypoperfused hemisphere was compared with the normally perfused hemisphere. **Results**: At the level of behavioral performance, the ACS group presented longer reaction times (RTs) for both flanker types. At the level of event-related potentials, patients in both the ACS and aICAS groups showed decreased N2 amplitudes in the parietal region of the hypoperfused hemisphere. They also showed reduced P300 amplitudes in the anterior frontal regions of both the hypoperfused and normally perfused hemispheres. Patients in the ACS group exhibited longer P300 latencies in the bilateral anterior frontal regions. In addition, both groups showed an increase in P300 amplitude in the central parietal region of the hypoperfused hemisphere. Notably, the aICAS group showed stronger compensatory capacity. **Conclusions**: ACS and aICAS patients exhibit different cognitive dysfunctions, with ACS patients presenting with more severe dysfunction of executive control. aICAS patients present with stronger compensatory capacity.

Keywords: internal carotid artery stenosis; intracranial arterial disorder; cognitive impairment; event-related potentials

1. Introduction

Carotid artery stenosis and intracranial atherosclerotic stenosis are two major causes of stroke worldwide [1,2]. Accumulated evidence has shown that asymptomatic carotid stenosis (ACS) can cause a variety of cognitive dysfunctions, including impairments in overall cognition, memory, and executive function [3]. Mechanisms associated with cognitive dysfunction include cerebral hypoperfusion and silent cerebral embolization [4,5]. On the other hand, limited data suggest a correlation between asymptomatic intracranial atherosclerotic stenosis (aICAS) and cognitive impairment [6]. Autopsy studies have revealed an increased incidence of intracranial atherosclerosis in patients with Alzheimer's disease (AD) [7,8]. Local and whole cerebral hypoperfusion and atherothrombotic embolization are the main pathogenic mechanisms [9,10]. Despite the similar mechanisms causing cognitive impairment, little is known about the degree of cognitive dysfunction associated with ACS and aICAS.

Neuropsychological cognitive tests have often been applied to assess cognitive function. However, these are unable to evaluate differences between the two cerebral hemispheres or to quantify the degree of cognitive decline [3,5]. They are also unable to identify the neurological mechanisms behind cognitive dysfunction. The event-related potential (ERP) technique is a noninvasive and quantitative method with high temporal resolution. Grimm *et al.* [11] reported that ERP is much more sensitive than psychological tests or electroencephalography in detecting metabolically-induced cognitive dysfunctions. Changes in ERP components reflect higher-order cognitive processes such as executive control and attention [12]. The amplitude and latency of voltage changes provide insights into the processing of information in the brain [13]. ERPs are an effective tool for detecting vascular cognitive impairment, in-

cluding transient ischemic attack (TIA), minor stroke [14], and cerebellar ischemic stroke [15]. ERPs are also effective at monitoring symptomatic improvement of vascular cognitive impairment resulting from transcranial direct current stimulation (tDCS) [16].

Executive control, also known as cognitive control, refers to higher-order cognitive functions that assess, regulate and optimize goal-directed behaviors by selecting, arranging, coordinating, and maintaining the basic processes of perception, memory, and action [17]. Executive functions include cognitive flexibility, working memory, and inhibition. Among these, inhibition is a central subcomponent of executive function [18,19]. The Eriksen flanker task has been used to study inhibition control [20]. Flanker tasks require that individuals disregard non-relevant task information and accurately react to a target stimulus presented centrally, amidst either matching or non-matching flanking stimuli. A previous study using the Eriksen flanker task found that the N2 and P300 components reflect inhibitory control [21]. The focus of the present study was therefore on the N2 and P300 components.

Here, we used the ERP technique to investigate the potential effects of aICAS and ACS on the cognitive functions of patients. Cognitive differences between the hypoperfused and normally perfused cerebral hemispheres were also compared in these patients. We tested two hypotheses in this study. First, whether there are differences in the N2 and P300 components between the disease and control groups, as well as between the ACS and aICAS groups. Second, whether there are differences in the N2 and P300 components between the hypoperfused and normally perfused cerebral hemispheres. To the best of our knowledge, this is the first study to investigate whether ACS and aICAS cause different levels of cognitive impairment. This research should provide valuable insights for improving the clinical management of cognitive impairment in ACS and aICAS patients.

2. Materials and Methods

2.1 Participants

G*power 3.1 software (Heinrich Heine University, Dïsseldorf, Nordrhein-Westfalen, Germany) [22] was used to calculate sample size in this study. The effect size was specified as Cohen's f = 0.25, which is considered a medium effect. The type I error margin (α) was considered 0.05. The power (1-β) was 0.8 based on a repeated measures ANOVA test. Because of the similar methodology, the study by Liu *et al*. [23] was taken into account when calculating the effect sizes. It was estimated that a minimum of 42 participants would be required overall, with at least 14 in each group.

From June 2024 to January 2025, 22 ACS patients and 15 aICAS patients hospitalized in the Department of Neurosurgery and Neurology at the Wuhan School of Clinical Medicine, Southern Medical University (China) were screened. aICAS was diagnosed as stenosis located in the intracranial segment of the internal carotid artery (ICA) (C6 or C7 segment) or middle cerebral artery (MCA) (M1 segment). ACS was diagnosed as a stenosis located at the beginning of the internal carotid artery. In addition, 23 participants who were matched to the stenosis group for age, gender, vascular risk factors (hypertension and diabetes) and years of education were also recruited for the control group. The inclusion criteria for patients were as follows: (1) age between 50 and 65 years; (2) unilateral severe ($\geq$70%) stenosis determined by computed tomography angiography (CTA) or digital subtraction angiography (DSA), with no stenosis on the opposite side. Normal vertebrobasilar system; (3) >6 years of education; (4) a Mini-Mental State Examination (MMSE) score $\geq$26; (5) no ischemic cerebrovascular events (e.g., transient ischemic attack or cerebral infarction) in the past 6 months; and (6) the patients were right-handed. The exclusion criteria were as follows: (1) a history of craniotomy and trauma; (2) a history of psychiatric disorders or neurological disorders; (3) not available for neuro-electrophysiological evaluation, or a noncoordinated evaluation process; and (4) a history of receiving medication that suppressed or activated the brain. This study was approved by the ethics committee of the General Hospital of Central Theater Command ([2024]008-01). All participants were fully informed before the examination and signed informed consent.

2.2 Neuropsychological Assessment

The MMSE [24] was utilized to evaluate general cognitive impairment, with a cutoff score of 26. Domain-specific cognitive functions were assessed using The Trail Making Test A (TMT-A) and B (TMT-B). The TMT-A score reflects information processing speed [25], while the TMT-B score reflects executive function [26].

2.3 Flanker Task

All participants performed a modified version of the Eriksen flanker task. This was administered via E-prime 2.0 software (Psychology Software Tools, Inc., Sharpsburg, PA, USA) on a computer screen. As shown in Fig. 1, the modified flanker paradigm consists primarily of five horizontally aligned arrows forming three stimulus types: (1) neutral—where the central arrow was flanked by a diamond; (2) congruent—with all arrows pointing in the same direction; and (3) incongruent—where the central arrow pointed opposite to the other arrows. Participants performed the task in a semi-dark, quiet room, seated 80 cm from the monitor with a white background and black stimuli. Instructed to respond quickly and accurately, they indicated the direction of the central arrow by clicking the left or right mouse button. Stimuli were presented for 1500 ms, with randomized interstimulus intervals (ISIs) ranging from 900 to 1100 ms. The task included 180 trials organized into three blocks of 60 trials each, with an equal distribution of the three stimulus types within each block [27].

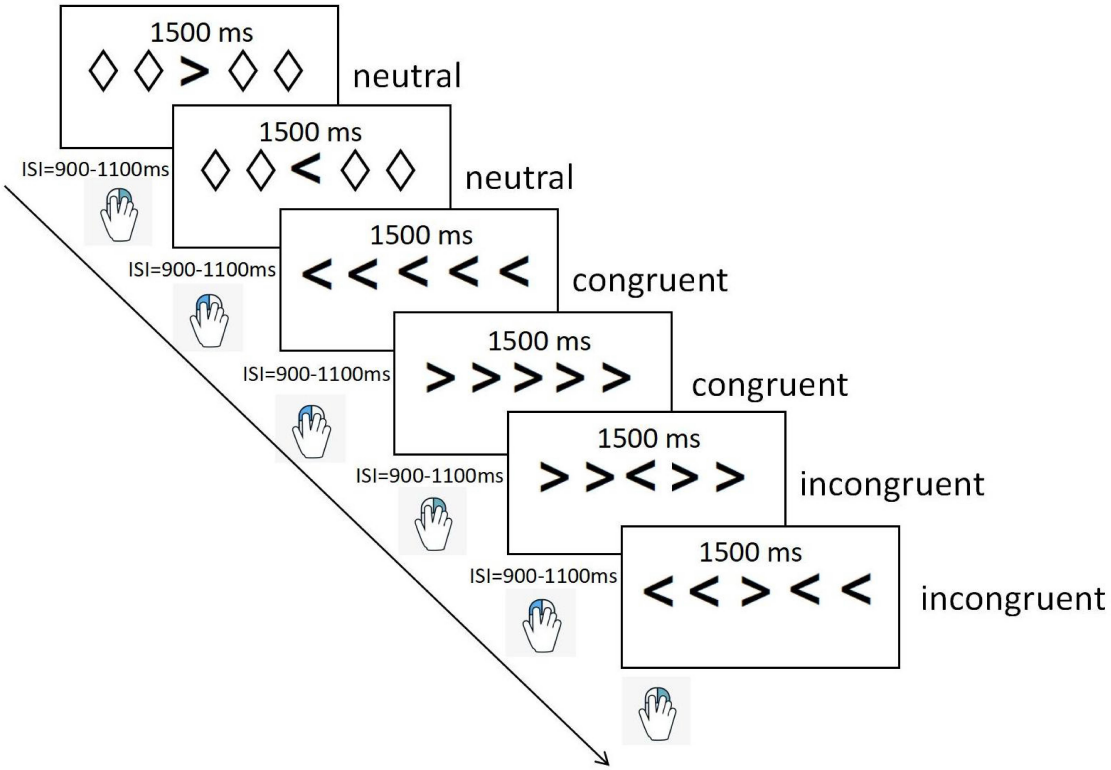

Fig. 1. Illustration of the experimental design. The modified Eriksen flanker task consisted of three blocks of 180 trials. Duration of the stimuli was 1500 ms. We used a random inter-stimulus interval (ISI) between 900 ms and 1100 ms. Each trial consisted of a display comprising a central arrow and two flanking stimuli on either side. Participants were instructed to press either the left or right mouse button to indicate the direction of the central arrow (left or right), while ignoring the flanking stimuli. For congruent and incongruent trials, the flankers were arrows pointing in the same or different direction, respectively, in relation to the central arrow.

2.4 Electroencephalography (EEG) Data Acquisition

EEG activity was registered using a 64-channel elastic cap outfitted with Ag/AgCl electrodes and an eegoTM amplifier (ANT Neuro, Inc., Hengelo, Overijssel, The Netherlands). Electrode placement adhered to the International 10–20 system. Online recordings employed CPZ electrode as a reference and were continuously digitized at a 1000 Hz sampling rate with a 0.5–40 Hz bandpass filter. Impedances for all electrodes were maintained below 5 kΩ. The anterior frontal zed (AFZ) electrode served as a grounding electrode. The variables "stenosis ipsilateral or contralateral" and "left or right hemisphere" were considered for each patient. For patients with stenosis on the right side, the examiner exchanged the electrodes of the left and right hemispheres so that left hemisphere electrodes were synonymous with the stenosis side for further analyses and illustrations. This procedure was not necessary for midline electrodes. Liu *et al.* [23] used ERPs to investigate deficits in cognitive control processes in frontal lobe injury via the same procedure.

2.5 EEG Data Analysis

Offline EEG data analysis was performed via EEGLAB, which is based on MATLAB (MATLAB R2022b, MathWorks Inc., Natick, MA, USA). The data first pass through a 0.5–40 Hz bandpass filter and a 50 Hz notch filter. Next, the epochs were extracted from –200 ms to 600 ms and locked to the stimuli. Baseline adjustment was conducted using the mean amplitude of the 200 ms pre-stimulus interval. Independent component analysis (ICA) was applied to eliminate vertical and horizontal ocular, muscular, and thermal activity artifacts. Epochs exceeding ±70 μV at any electrode were rejected before averaging. Consistent with most of the literature [23,27,28], the EEG data were further rereferenced with the common average.

The negative deflection in ERP that appeared between 180 and 250 ms post-stimulus was identified as N2. P300 was recognised as the most positive deflection in the ERP between 300 and 500 ms post-stimulus. The peak latency and mean amplitude of N2 and P300 were measured for each subject. The N2 and P300 mean amplitudes were calculated in the 50 ms and 150 ms time windows around the ERP peak point, respectively. The latencies of N2 and P300 correspond to the latencies of the maximal peaks of N2 and P300, respectively, measured from the beginning of the stimulus. Most studies consider N2 to be maximal in the fronto-central sites, and P300 over parietal sites

Table 1. Demographic information on the three groups.

Variable	CG (n = 23) Mean (SD)	ACS (n = 22) Mean (SD)	aICAS (n = 15) Mean (SD)	F/χ^2	p	Follow-up analysis[a]
Age (years)	55.48 (4.94)	59.00 (6.30)	56.60 (5.29)	2.319	0.108	ns
Sex (female/male)	5/18	3/19	1/14	$\chi^2_{0.05,2} = 1.668$	0.434	NA
TMT-A	53.48 (16.06)	75.68 (19.86)	69.33 (21.14)	8.212	0.001	0.001[b] 0.042[c]
TMT-B	50.13 (15.31)	66.96 (16.63)	63.80 (22.31)	5.588	0.006	0.007[b] 0.071[c]
Hypertension	13	14	11	$\chi^2_{0.05,2} = 1.106$	0.575	NA
Diabetes	8	8	5	$\chi^2_{0.05,2} = 0.037$	0.982	NA
Smoking	9	12	3	$\chi^2_{0.05,2} = 4.447$	0.108	NA
Alcohol	8	6	1	$\chi^2_{0.05,2} = 3.923$	0.141	NA
Education (years)	8.48 (2.15)	9.91 (2.71)	9.00 (3.21)	1.667	0.198	ns
MMSE	29.09 (0.60)	28.59 (1.10)	28.33 (1.23)	2.985	0.058	ns

CG, control group; ACS, asymptomatic carotid stenosis; aICAS, asymptomatic intracranial atherosclerotic stenosis; SD, standard deviation; MMSE, Mini-Mental State Examination; ns, not significant; NA, not applicable; TMT-A, Trail Making Test A; TMT-B, Trail Making Test B.

[a]Follow-up analysis based on Bonferroni correction.

[b]p-value between ACS and CG in Bonferroni correction.

[c]p-value between aICAS and CG in Bonferroni correction.

[29,30]. However, with aging the scalp topography of N2 and P300 tends to shift posteriorly and anteriorly, respectively [31–33]. Based on these relevant studies and our visual inspection of the corresponding topographical maps, we quantified N2 at parietal electrodes (P3, Pz, P4) and P300 at anterior-frontal electrodes (AF3, AF4). No data were recorded since the AFZ was used as the grounding electrode. Because the patient group(s) showed a more centro-parietal P300 distribution than the control group, we also analyzed mean P300 amplitudes at centro-parietal sites (CP3, CPZ, CP4). The electrodes located at P3, AF3, and CP3 indicated the hypoperfused hemisphere, whereas the electrodes at P4, AF4, and CP4 indicated the normally perfused hemisphere.

2.6 Statistical Analyses

All statistical analyses were performed with SPSS V.27 (IBM, Armonk, NY, USA). A p-value < 0.05 was considered significant.

Differences in age, years of education, and neuropsychological scale (MMSE, TMT-A, TMT-B) were determined with one-way analysis of variance (ANOVA). Differences in sex, diabetes status, hypertension status, and history of smoking between the control group and patient groups were assessed with the chi-square test.

Behavioral performances were carried out by 3 (Group: ACS, aICAS, and control) $\times$ 2 (Type: congruent, incongruent) repeated-measures ANOVA. Peak latencies and mean amplitudes of N2 and P300 components were analyzed by 3 (Group: ACS, aICAS, control) $\times$ 2 (Type: congruent, incongruent) $\times$ 3 (Laterality: hypoperfused hemisphere, midline, normally perfused hemisphere) repeated-measures ANOVA. Greenhouse–Geisser corrections were applied where necessary. Bonferroni corrections were applied to correct for multiple comparisons.

3. Results

3.1 Demographic Information

A total of 37 patients were recruited: 22 with ACS and 15 with aICAS. The control group (CG) comprised 23 matching participants. No significant differences in demographic factors were observed between the three groups (Table 1). During EEG data preprocessing, one participant in the CG was excluded from the study because of excessive signal noise in the EEG data.

3.2 Results of Neuropsychological Assessment

No significant difference in MMSE scores were observed between the three groups (Table 1). The TMT-A (p = 0.001) and TMT-B (p = 0.006) scores were both significantly higher in the patient groups than in the CG. Both the ACS (p = 0.001) and aICAS (p = 0.042) groups had higher TMT-A scores than the CG, whereas only the ACS group (p = 0.007) had higher TMT-B scores than the CG.

3.3 Behavioral Results

3.3.1 Accuracy

For the flanker effect, accuracy analysis revealed a significant main type effect (F = 4.769, p = 0.033, η^2 = 0.076), a non-significant main group effect (F = 2.303, p = 0.109, η^2 = 0.074), and no group $\times$ type interaction effect (F = 0.323, p = 0.725, η^2 = 0.011) (Table 2). For both the ACS and aICAS groups, patients showed more errors in incongruent trials than in congruent trials (98.7% vs. 98.00%). There were no differences between groups across types.

Table 2. Behavioral comparisons between the CG, ACS, and aICAS groups.

		CG (n = 23) Mean (SD)	ACS (n = 22) Mean (SD)	aICAS (n = 15) Mean (SD)		F	*p*	Bonferroni correction	Partial η^2
RT (ms)	Con	612.650 (15.083)	716.975 (15.083)	619.157 (18.677)	Group	14.325	<0.001	<0.001[a] 0.774[b]	0.331
	Incon	612.710 (15.184)	718.778 (15.184)	620.093 (18.803)	Type	4.098	0.048		0.066
ACC (%)	Con	0.988 (0.988)	0.966 (0.009)	0.984 (0.011)	Group	2.303	0.109		0.074
	Incon	0.997 (0.006)	0.976 (0.006)	0.988 (0.008)	Type	4.769	0.033		0.076

RT, reaction time; ACC, accuracy; Con, congruent; Incon, incongruent.

[a]*p*-value between ACS and CG in Bonferroni correction.

[b]*p*-value between aICAS and CG in Bonferroni correction.

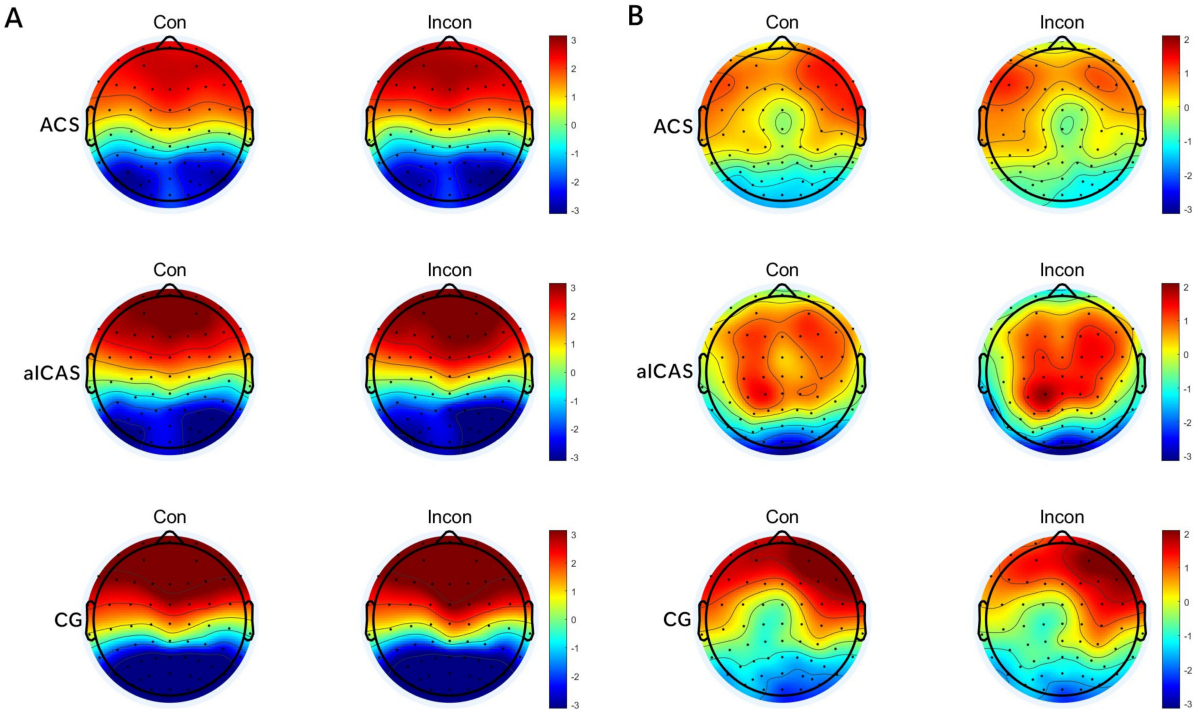

Fig. 2. N2 and P300 topographies of each type in both groups. (A) N2 topographies in the three groups. (B) P300 topographies in the three groups.

3.3.2 Reaction Time

Significant differences in RT were observed between the three groups (F = 14.325, $p < 0.001$, $\eta^2 = 0.074$) (Table 2). Further testing revealed that the RT in the ACS group (M = 717.876 ms) was longer than that in the aICAS group (M = 619.625 ms, $p < 0.001$) and the CG (M = 612.680 ms, $p < 0.001$). No significant difference was found between the aICAS group and the CG. A significant type effect (F = 4.098, $p = 0.048$) was also observed, but there was no difference in the group × type interaction effect (F = 1.406, $p = 0.253$). Further analysis revealed that patients in the ACS group exhibited a slower RT in the incongruent condition (M = 718.778 ms) than in the congruent condition (M = 716.975 ms; $p = 0.017$). No such difference was observed in the other two groups. Compared with congruent conditions, only the ACS group presented RTs under incongruent conditions.

3.4 Results for Event-Related Potential

3.4.1 Scalp Topography

Fig. 2 shows the scalp topography of the N2 and P300 components. The N2 component has a maximum amplitude distribution in the parietal region, whereas the P300 component has a maximum amplitude distribution in the frontal region.

3.4.2 P300

Significant group (F = 5.483, $p = 0.007$, $\eta^2 = 0.164$) and laterality (F = 23.139, $p < 0.001$, $\eta^2 = 0.292$) effects were observed for P300 amplitude in the anterior frontal region. No significant group × laterality interaction effect was found (F = 1.514, $p = 0.211$; $\eta^2 = 0.051$). Post hoc analysis revealed lower P300 amplitudes in the bilateral anterior frontal regions (normally perfused hemisphere and hypoperfused hemisphere) in both the ACS and aICAS

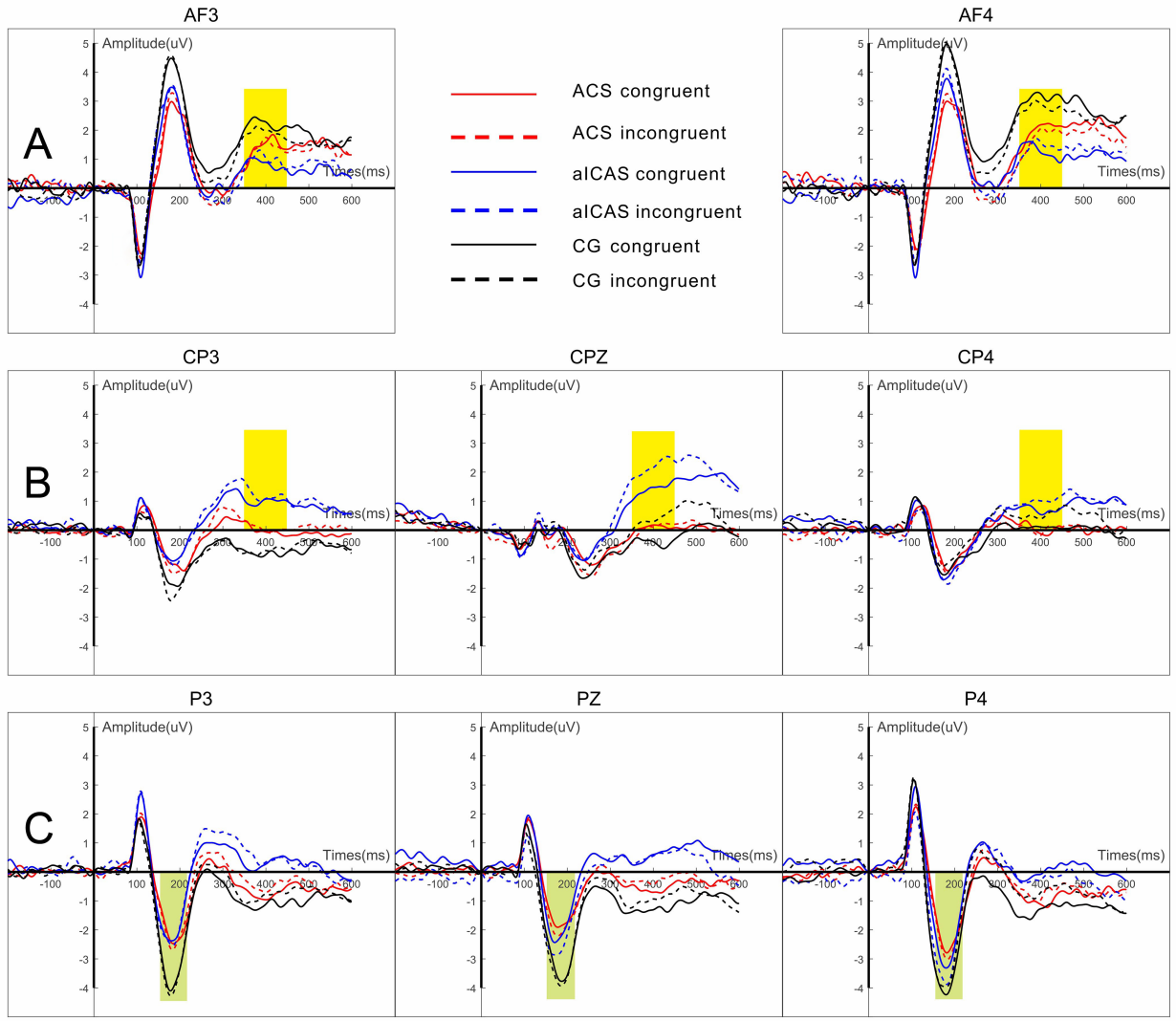

Fig. 3. Grand-averaged ERP of the N2 and P300 waveforms. Green and yellow rectangles index the time windows for N2 (170–220 ms) and P300 (350–450 ms) amplitude analysis, respectively. (A) Averaged P300 waveform comparisons of the hypoperfused hemisphere (AF3) and normally perfused hemisphere (AF4) in anterior frontal regions. (B) Averaged P300 waveform comparisons of the hypoperfused hemisphere (CP3), midline (CPZ), and normally perfused hemisphere (AF4) in central parietal regions. (C) Averaged N2 waveform comparisons of the hypoperfused hemisphere (P3), midline (PZ), and normally perfused hemisphere (P4) in parietal regions.

groups compared with the CG (Figs. 3,4). No significant difference in P300 amplitudes were observed between the ACS and aICAS groups. Further analysis revealed a significant group effect (F = 8.727, $p < 0.001$, $\eta^2 = 0.238$) and laterality effect (F = 5.474, $p = 0.023$, $\eta^2 = 0.089$) on P300 latencies, but no significant group $\times$ laterality interaction effect (F = 0.523, $p = 0.595$, $\eta^2 = 0.038$). Post hoc analysis revealed delays in P300 latencies in the bilateral anterior frontal regions (normally perfused hemisphere and hypoperfused hemisphere) in the ACS group compared to both the CG and aICAS group. No significant differences were observed between the CG and aICAS group. Both the ACS and aICAS groups presented similar decreases in P300 amplitude in the anterior frontal regions of the hypoperfused and normally perfused hemispheres. However, only the ACS group exhibited longer P300 latencies in the bilateral anterior frontal regions.

P300 amplitudes in the central parietal region showed a significant main group effect (F = 7191, $p = 0.002$, $\eta^2 = 0.204$). Post hoc analysis revealed increased P300 amplitudes in the central parietal region of the hypoperfused hemisphere in both the ACS and aICAS groups compared to the CG. The aICAS group also showed increased P300 amplitudes at the midline. Furthermore, P300 amplitudes were significantly different between the ACS and aICAS groups in the hypoperfused hemisphere, with the aICAS group exhibiting greater amplitudes (Figs. 3,4).

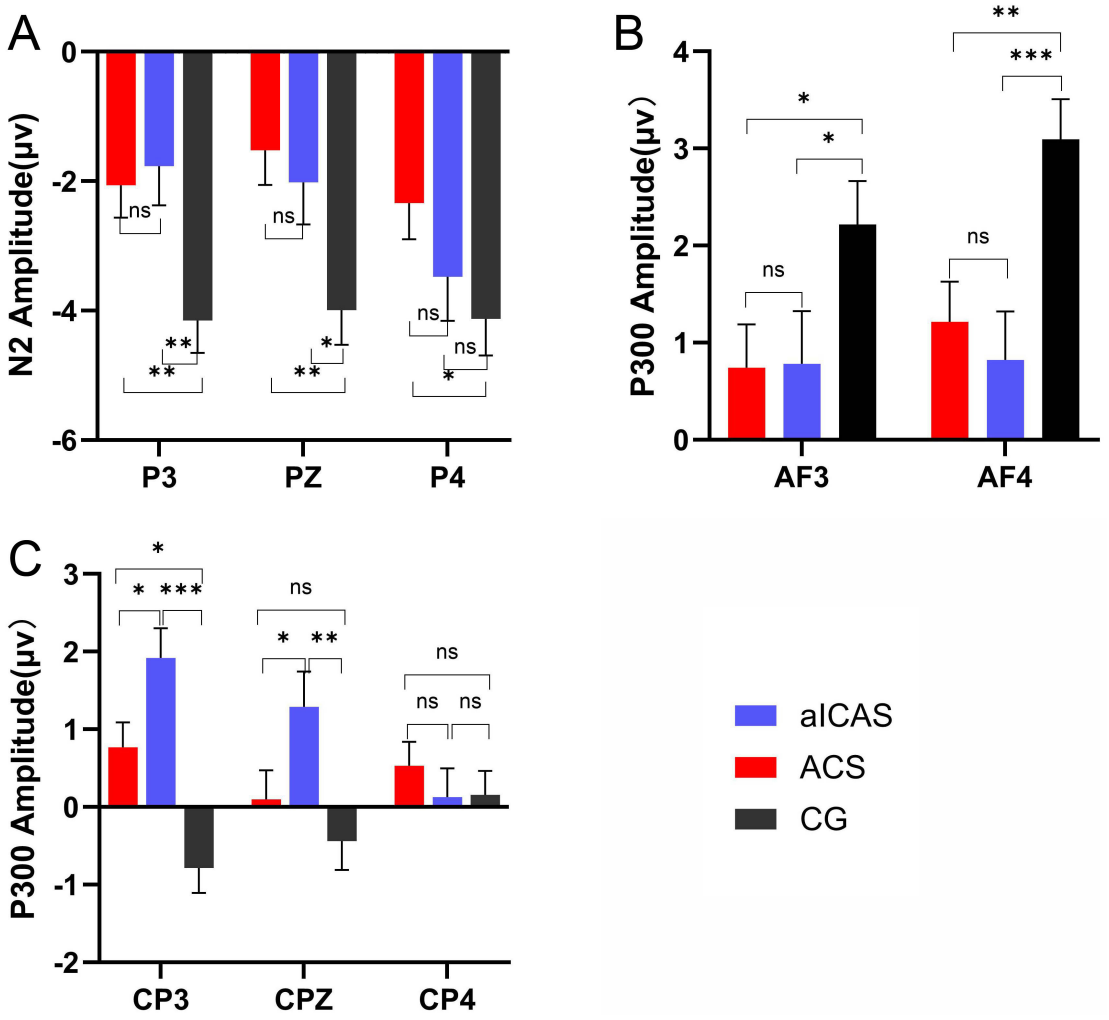

Fig. 4. Results of statistical analysis for the N2 and P300 amplitudes. (A) Comparison of N2 amplitudes between the three groups at different cerebral hemispheres of the parietal regions. (B) Comparison of P300 amplitudes between the three groups at different cerebral hemispheres of the anterior frontal regions. (C) Comparison of P300 amplitudes between the three groups at different cerebral hemispheres of the central parietal regions (CP3, hypoperfused hemisphere; PZ, midline; CP4, normally perfused hemisphere). ns, not significant; *: $p < 0.05$; **: $p < 0.01$; ***: $p < 0.001$.

3.4.3 N2

For N2 amplitude, significant differences were seen for group effect (F = 5.067, $p = 0.009$, $\eta^2 = 0.153$), laterality effect (F = 7.805, $p = 0.002$, $\eta^2 = 0.112$), and group $\times$ laterality interaction effect (F = 2.858, $p = 0.033$, $\eta^2 = 0.093$). Post hoc analysis revealed significantly decreased N2 amplitudes in the hypoperfused hemisphere and midline in both the ACS and aICAS groups compared to the CG. Decreased N2 amplitudes were also observed in the normally perfused hemisphere in the ACS group. No significant differences in N2 amplitudes were observed between the ACS and aICAS groups in the hypoperfused hemisphere or midline (Figs. 3,4). Similar decreases in N2 mean amplitudes were seen in both the ACS group and the aICAS group in the parietal region of the hypoperfused hemisphere and the midline. No significant group effect was observed for N2 latency (F = 2.493, $p = 0.092$, $\eta^2 = 0.082$).

4. Discussion

The present study sought to investigate the effects of ACS and aICAS on inhibitory control via electrophysiology. Both ACS and aICAS were found to have a close association with inhibitory control dysfunction, with greater severity in the ACS group. Compared to the aICAS group, the ACS group showed decreased N2 amplitude in a broader region, extended P300 latencies in the bilateral anterior frontal regions, longer RTs in behavioral performance, and a smaller compensatory capacity in the central parietal region of the hypoperfused hemisphere. Both the ACS and aICAS groups have developed compensatory mechanisms in the central parietal region of the hypoperfused hemisphere. This phenomenon can be referred to as functional plasticity, with the aICAS group showing a greater compensatory capacity.

Hypoperfusion caused a decrease in P300 amplitudes and increased latencies in the ipsilateral anterior frontal region. It also decreased N2 amplitudes in the ipsilateral parietal region, leading to the same changes in the normally perfused hemisphere. A compensatory mechanism was identified in the central parietal region of the hypoperfused hemisphere, but not in the normally perfused hemisphere.

The behavioral results revealed the ACS group had longer RTs than the aICAS and control groups. Both the ACS and aICAS groups exhibited significant differences in accuracy and RTs between congruent and incongruent trials, indicating the flanker task successfully induced interference control in the presence of conflicting stimuli. ACS and aICAS patients performed with similar accuracy to the CG, suggesting the task may be relatively simple [27]. The longer ISI employed in our study allowed sufficient time for the patients to adapt [34]. The prolongation of RTs indicates that supplementary cognitive control mechanisms are engaged when participants encounter incompatible stimuli [35]. To match the accuracy of the CG, the ACS group required more time to complete the reaction process. The same pattern of longer RT but equivalent accuracy during the performance of a flanker task was reported previously in patients with prolactinomas [27]. Therefore, prolonged RT is reliable behavioral evidence of impaired interference control in patients with ACS. No significant difference in RT was observed between aICAS patients and controls, which may be attributed to the simplicity of the task.

N2 in inhibitory control paradigms may be associated with premotor inhibitory processes and conflict monitoring. Although the N2 component was traditionally thought to have a fronto-central distribution [30], the results of scalp topography in the present study revealed that it was most prominent in the parietal region (Fig. 2A). This shift in N2 distribution, known as age-related posteriorization, was consistent with findings from prior research [28,36]. The shift may be due to the reduced efficiency of the frontal lobe in the process of action inhibition, which requires the recruitment of additional parietal circuits [28]. The amplitude of the parietal N2 component reflects the capacity to recruit additional parietal circuits, with decreased efficiency of inhibitory control over the frontal region with age. Stronger N2 amplitudes indicate a stronger ability to recruit additional parietal circuits. In the present study, decreased N2 amplitudes were observed in the parietal region and midline of the hypoperfused hemisphere in patients with aICAS, and in the bilateral parietal region in patients with ACS. These findings suggest the ability of parietal regions to recruit additional parietal circuits was affected, leading to a decrease in inhibitory control. The ACS group presented a broader region of decreases in N2 amplitudes and a more significant decline in inhibitory control function.

For the P300 component, the scalp topography was mainly distributed in the frontal region (Fig. 2B), whereas most studies have reported its distribution in the central-parietal regions [37]. The P300 component is associated with attentional control processing [38] and with aspects of executive functioning, such as updating the working memory, subsequent memory storage, inhibitory control, and selective attentional processes [39]. The change in topographical scalp distribution of the P300 component is associated with aging, as shown by Lucci *et al*. [31]. These authors demonstrated the impact of aging on conflict detection via a GO-NOGO paradigm, observing a shift toward frontal region dominance in elderly individuals. Similar findings have been reported in functional neuroimaging studies of cognitive aging. This posterior-to-anterior shift in aging (PASA) has typically been attributed to functional compensation [40].

In the present study, the aICAS and ACS groups showed decreased P300 amplitudes in the anterior frontal regions of both the hypoperfused and normally perfused hemispheres. P300 amplitude is thought to indicate the inhibition of irrelevant neuronal activity to enhance attentional processing [29]. Changes in P300 amplitude reflect variations in the amount of attentional resources allocated to a task, with larger amplitudes indicating increased attentional resources [41]. As the P300 amplitude decreases, aICAS and ACS patients lose their ability to access their attention resources. Similar findings have been reported regarding the effects of other disorders on cognitive function. For example, children with a history of concussion show a decrease in P3b amplitude, which reduces their ability to allocate attentional resources [42]. Bejr-Kasem *et al*. [43] reported reduced P300 amplitudes in patients with Parkinson's disease combined with dementia. Numerous studies have shown abnormalities/differences in P300 amplitude in patients with both mild cognitive impairment and Alzheimer's disease [44].

Both the aICAS and the ACS groups showed an increase in P300 amplitude in the central and parietal regions of the hypoperfused hemisphere, as well as in the midline. An increased P300 amplitude indicates the use of abnormal attentional resources to compensate for brain dysfunction [45]. This finding also reflects the functional plasticity of the hypoperfused hemisphere. It has been suggested that both ACS and aICAS patients develop compensatory mechanisms in the central parietal region of the hypoperfused hemisphere, with aICAS patients demonstrating stronger compensatory capacity.

P300 latency reflects neurocognitive processing, with prolonged latency of this endogenous component being associated with memory dysfunction [46]. The ACS group displayed longer P300 latencies in the bilateral anterior frontal regions, suggesting these patients may have experienced more severe cognitive impairment than aICAS patients.

The greater P300 amplitude in the aICAS group also suggests the development of more effective functional plasticity. There are two possible reasons for this. First, severe

ACS may impair the development of collaterals required to compensate for hypoperfusion [47,48], leading to a state of dysautoregulation [49]. Second, the aICAS lesion is located more distally, allowing the development of collaterals from the proximal site of the unoccluded artery [50].

Reduced N2 and P300 amplitudes were observed in the bilateral cerebral hemispheres, which may be associated with haemodynamic impairment on the contralateral side due to reduced perfusion pressure and inefficient collateral circulation. This is consistent with the findings of Dacic *et al.* [51], who used arterial spin labelling magnetic resonance imaging (MRI) to show that patients with asymptomatic unilateral carotid stenosis suffered significant bilateral cerebral hypoperfusion. Functional magnetic resonance imaging studies have also shown that unilateral carotid artery stenosis leads to a reduction in functional connectivity between the two cerebral hemispheres. He *et al.* [52] reported that the decline in functional connectivity in patients with left carotid artery stenosis was concentrated in the bilateral inferior frontal gyri and temporal lobes. They also found that reduced connectivity between brain regions was significantly associated with cognitive impairment.

The present study is the first to demonstrate the existence of different cognitive dysfunctions in ACS and aICAS patients from a neuro-electrophysiological point of view, and to reveal the neural mechanisms behind these dysfunctions. The ACS group showed extensive impairments, as evidenced by decreased N2 amplitude across a broad region, extended P300 latencies in bilateral anterior frontal regions, longer RTs in behavioural performance, and reduced compensatory capacity in the central parietal region of the hypoperfused hemisphere. This study introduces a novel method for assessing cognitive functions in ACS and aICAS, providing reproducible results while mitigating the learning effect. It is also expected to be an effective tool for assessing cognitive function after revascularisation.

Our study has several limitations. First, the absence of multimodal validation (e.g., perfusion MRI and Doppler ultrasound) meant that changes in intracranial perfusion could not be correlated with ERP components. This would provide more direct evidence that hypoperfusion causes vascular cognitive dysfunction. Second, the modest sample size limits the generalisability of the findings. In order to validate our results, future studies should be multicentred and larger in scale. Third, longitudinal assessment of cognitive changes after treatment or progression of stenosis is lacking, and only limited research has been conducted on the potential reversibility of cognitive dysfunction in these individuals. Long-term follow-up should help to understand the effects of different treatment modalities (medical therapy and revascularisation) on cognitive function. This will provide a basis for choosing appropriate treatment modalities for ACS and aICAS with regard to cognitive improvement.

5. Conclusions

The present study provides behavioral and neuro-electrophysiological evidence of impaired inhibitory control in patients with aICAS and ACS. The hypoperfused hemisphere caused a decrease in P300 amplitudes and increased latencies in the ipsilateral anterior frontal region, as well as a decrease in N2 amplitudes in the ipsilateral parietal region. This also led to the same changes occurring in the normally perfused hemisphere. Compared with the aICAS group, the ACS group presented more severe dysfunction of executive control, as evidenced by longer reaction times in behavioral performance, extended P300 latencies in the bilateral anterior frontal regions, and decreased N2 amplitudes in the broader region. Both the ACS and aICAS groups develop compensatory mechanisms in the central parietal region of the hypoperfused hemisphere, with the aICAS group showing stronger compensatory capacity. Moreover, both groups showed increased P300 amplitudes in the central and parietal regions of the hypoperfused hemisphere, as well as in the midline. The aICAS group exhibited larger P300 amplitudes than the ACS group.

Abbreviations

ACS, Asymptomatic carotid stenosis; aICAS, asymptomatic intracranial atherosclerotic stenosis; ERP, event-related potential; MMSE, Mini-Mental State Examination; CTA, computed tomography angiography; DSA, digital subtraction angiography; TMT-A, Trail Making Test A; TMT-B, Trail Making Test B.

Availability of Data and Materials

The datasets generated for this study can be obtained by contacting the corresponding author.

Author Contributions

JS and GX were responsible for the conceptualization; FW, ZR and PZ were performed the neurophysiological experiments and neuropsychological assessments. FW and HL were contributed to the formal analysis and investigation. PZ was contributed to the project administration. HL was completed the original draft. JS and GX were critically supervised the draft. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee at the General Hospital of Central Theater Command (Wuhan, China) ([2024]008-01). All of the study's participants have signed informed consent forms.

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Conflict of Interest

The authors declare no conflict of interest.

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