Response inhibition alterations in migraine: An event-related potential study

Guoliang Chen
Chinese PLA General Hospital
Yansong Li
Nanjing University
Dong Zhao
Chinese PLA General Hospital
Rongfei Wang
Chinese PLA General Hospital
Dengfa Zhao
Chinese PLA General Hospital
Ignacio Obeso
HM CINAC
Shengyuan Yu (yusy1963@126.com)
Chinese PLA general hospital https://orcid.org/0000-0002-3961-2464

Research article

Keywords: Migraine, Response inhibition, ERPs, N2, P3, Theta oscillation, Delta oscillation, Cortical hyperexcitability

Posted Date: August 5th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-52866/v1

Version of Record: A version of this preprint was published on October 2nd, 2020. See the published version at https://doi.org/10.1186/s10194-020-01187-2.

Abstract

Background

Migraine is characterized by a hypersensitivity to environmental stimulation which climaxes during headache attacks but persists during attack-free period. Despite ongoing debates about the nature of the mechanisms giving rise to this abnormality, the presence of deficient inhibitory cortical processes has been proposed to be one possible mechanism underlying its pathogenesis. Empirical evidence supporting this notion is mainly based on previous findings showing functional cortical hyperexcitability in the sensory domain. Considering that a general inhibitory control process can play an important role across early to later stage of information processing, this may in turn indicate the important role other dimensions of inhibitory control can play in migraine disability. To this end, the present study was designed to examine the pathophysiological basis of inhibitiory control that takes place during suppression of prepotent responses.

Methods

Twenty-two patients with migraine without aura (mean age = 30.86 ± 5.69 years; 19 females) during the interictal period and 25 healthy controls (mean age = 30.24 ± 3.52 years; 18 females) were recruited. We employed a stop signal task in combination with event-related potentials (ERPs) to examine participants' neural activity supporting response inhibition.

Results

Behaviorally, migraineurs exhibited prolonged reaction times to the stop signal relative to healthy controls. At the neural level, the amplitude of the stop-N2, a component of the ERPs related to conflict monitoring during early, non-motoric stages of inhibition, was significantly increased in migraineurs. Meanwhile, the amplitude of the stop-P3, a component of the ERPs reflecting late-stage inhibition of the motor system itself and cognitive evaluation of motor inhibition, was also significantly increased in migraineurs. Moreover, our time-frequency analysis has further revealed increased delta activity in the time window used to extract the mean amplitude of the stop-P3 in migraineurs relative to healthy controls.

Conclusions

Consistent with the theory that cortical hyperexcitability is a key signature of migraine, these findings revealed a decrease in suppressing prepotent responses in migraineurs, which can be attributable to cortical hyperexcitability. These novel findings imply the existence of dysfunctional inhibitory control at later stage of information processing.

Introduction

Migraine is a common episodic neurological disorder which is mainly characterized by recurrent attacks of headache, which has a great detrimental influence on quality of life (1, 2). The annual prevalence of migraine estimated in the worldwide population were around 9% and migraine predominantly affects females (3–6), resulting in an increasing financial burden on global economies (7, 8). Given such a situation, considerable empirical efforts have been devoted into understanding the causes of migraine because it would help with identifying risk factors, establishing correct diagnosis and developing a range of effective therapeutic interventions (9). Although the exact pathogenetic mechanisms for migraine have not been completely elucidated, migraine, at its core, is suggested to be a complex brain disorder (10, 11). To search for evidence of brain dysfunction in migraineurs, measuring neural activities with electrophysiological methods (i.e., Electroencephalogram (EEG)) has been proven to be effective in improving our understanding on the physiopathology of the migraine brain (12–15).

The majority of electrophysiological studies on stimulus responsivity in visual, auditory, somatosensory and nociceptive domains strongly suggest that migraine is associated with a state of functional cortical hyperexcitability after sensory stimulation and a lack of the physiological habituation to repeated sensory stimulation especially during the intervals between attacks (12, 16, 17). Despite ongoing debates about the nature of the mechanisms giving rise to these abnormalities (10, 18), the presence of deficient inhibitory cortical processes has been argued to be one possible mechanism underlying the pathogenesis of these conditions (18, 19). Available evidence supporting this claim has come mainly from previous studies on the cortical response to external sensory stimuli in migraineurs (12, 16, 20, 21). For example, reliable differences in cortical excitability in response to sensory stimulation between migraineurs and healthy controls have been found, usually reflected by increased amplitude of evoked responses (19, 22, 23) and decreased activity of GABA-mediated inhibition of the sensory cortex (24). Given that inhibitory control does not take place only at the sensory level and can play an important role across early to later stage of information processing (25, 26), it is tempting to understand the possible role of other dimensions of inhibition control, such as inhibition of an initiated response, can play in migraine disability. However, to date, it is somewhat surprising that few researchers have turned their attetion in this direction.

To address this issue, the present study was designed to examine neural activity supporting response inhibition by using a stop-signal task (SST) in combination with event-related potentials (ERPs) in patients with migraine without aura (MwoA) during the interictal period. The stop-signal task is a typical paradigm for measuring inhibitory control of an ongoing motor response (27, 28). In this experimental paradigm, participants are instructed to respond quickly and efficiently to a primary Go stimulus while inhibiting their go responses when a Go stimulus is occasionally and unexpectedly followed by a stop-signal. Considering that the promise of ERP-based biomarkers of cognitive dysfunction has been increasingly recognized in psychiatric (29, 30) and neurological disorders (31) including migraine (12, 14, 15), the usage of this technique can thus greatly help in examining how the brain detects the stop signal and decides to stop a prepotent motor response in migraineurs. Previous ERP studies have consistently

identified two typical ERP components related to response inhibition: the stop-N2 and stop-P3. The stop-N2 refers to a negative wave that occurs 200–300 ms following a stop signal, with its maximum amplitude over frontocentral, central and centroparietal scalp regions, while the stop-P3 is a large positive wave that peaks around 300–600 ms following a stop signal, with its maximum amplitude over central and centroparietal locations (32). In spite of some debates about the functional significance of these two components, they are considered to reflect different sub-processes that underline response inhibition. Specifically, the stop-N2 is proposed to primarily reflect conflict monitoring during early, non-motoric stages of inhibition, while the stop-P3 is mainly thought to reflect late-stage inhibition of the motor system itself and cognitive evaluation of motor inhibition (32–35). Given that common time-domain ERP measures may not accurately reflect multiple processes underlying response inhibition, the use of time–frequency (TF) analysis can provide complementary information about underlying processes behind the stop N2–P3 complex in response inhibition. Indeed, event -related theta (4–8 Hz) and delta (1–4 Hz) oscillations have been argued to index two separable, but highly overlapping processes underlying the stop N2–P3 complex in response inhibition, although their functional significance has yet to be fully clarified (32, 36). Given that deficits in sensory inhibition and inhibitory attentional control have been reported in migraineurs (12, 37), one could expect that patients with MwoA display a deficit in response inhibition as evidenced by prolonged reaction times to a stop signal and by increased amplitudes of both stop-N2 and stop-P3. Moreover, time–frequency decomposition has been employed to characterize separable but overlapping processes underlying the stop N2–P3 complex in response inhibition in patients with MwoA.

Methods

Participants

In the present study, 22 patients with MwoA (age = 30.86 ± 5.69 years; 19 females) and 25 healthy controls (age = 30.24 ± 3.52 years; 18 females) were recruited. All participants had normal or corrected-to-normal vision and were right-handed. Both groups were matched on the basis of sex, age and years of education. For healthy controls, they reported no history of neurological or psychiatric disorders and no migraine in first-degree relatives. For patients with MwoA, they underwent neurologic and physical evaluations by trained neurologists (Z.D. and S.Y.) as well as standard neuropsychological assessment by neuropsychologists (G.C.). The inclusion criteria for patients were used: 1) fulfilling the diagnosed criteria for migraine without aura according to the International Classification of Headache Disorders, 3rd edition (ICHD-3); 2) at least 2 year's history of migraine and at least one migraine episode per month; 3) no migraine attacks 72 h before and after the experiment and 4) outside migraine attacks during the experiment (the interictal period). Moreover, the following exclusion criteria were used: 1) neurological diseases (i.e., epilepsy, neuromuscular disorders); 2) psychiatric symptoms (i.e., anxiety and depression); 3) mental retardation; 4) a current or past history of substance dependence, 5) receiving prophylactic anti-migraine therapy and 6) having suicide ideation and/or previous suicide attempts; 7) the presence of periodic limb movement disorder (i.e., nocturnal hyperkinesias) and recurrent parasomnias (> 3 episodes

per week). All female participants took no oral contraceptives for at least 1 week. Demographic and clinical characteristics are described in Table 1.

Table 1
Demographic and clinical characteristics of the study sample

	MwoA (n = 22)	Controls (n = 25)	Group comparison
	(M ± SEM)	(M ± SEM)	
Age, years	30.86 ± 1.21	30.24 ± 0.70	$t(45) = -0.46, p > 0.05$
Gender (F/M)	(19/3)	(18/7)	$\chi^2 = 2.40, p > 0.05$
Education, years	15.55 ± 0.59	15.32 ± 0.45	$t(45) = -0.31, p > 0.05$
BMI [kg/m^2]	21.09 ± 0.77	21.04 ± 0.52	$t(45) = -0.06, p > 0.05$
SAS	44.43 ± 2.27	39.45 ± 1.49	$t(45) = -1.88, p > 0.05$
SDS	44.67 ± 2.97	42.85 ± 2.13	$t(45) = -0.51, p > 0.05$
Duration of migraine, hours	30.61 ± 5.47		
History of migraine, years	12.41 ± 1.34		
Migraine frequency, times per month	5.00 ± 0.92		
Severity of headache (VAS scale)	8.23 ± 0.25		

VAS, visual analog scale, with 0 indicating no pain and 10 worst possible pain; SAS, Self-Rating Anxiety Scale; SDS, Self-Rating Depression Scale; BMI, body mass index

All participants volunteered to participate in the present study. They all signed consent forms and the Ethics Committee of the Chinese PLA General Hospital approved the study protocol.

Stop-signal task

We used the SST to measure participants' response inhibition, which is similar to that described in previous studies (27, 38). This task included 80% Go trials and 20% Stop trials (Fig. 1). On Go trials, participants were presented with a fixation cross on a black computer screen lasting for 600–800 ms, which is immediately followed by a visual stimulus (the letter 'X' or 'O') (a Go signal) lasting for 1000 ms. Participants were instructed to judge the shape of the visual stimulus as accurately and quickly as possible via a button press with the index fingers of the left and right hands, which was counterbalanced across participants. On the remaining Stop trials, the stop stimulus (a red square appearing above the location of the go stimulus) appeared after the Go stimulus after a variable delay of 0-250 ms in steps of 50 ms (stop signal delay; SSD), cuing participants to withhold their responses to the Go stimulus. Each trial was followed by a blank screen for a variable intertrial interval (1500–2000 ms). There were totally

four experimental blocks of 400 trials. The experiment was preceded by a short practice block. Task presentation was controlled via E-prime 2.0.

EEG data recording and analysis

EEG data recording procedure is similar to that described in our previous studies (39, 40). Specifically, EEG was recorded (SynAmps amplifier, NeuroScan) with a quick cap carrying 64 Ag/AgCl electrodes placed at standard locations covering the whole scalp (the extended international 10–20 system). The reference electrode was attached to the right mastoid (M2), and the ground electrode was placed on the forehead. The vertical electrooculogram (VEOG) was recorded with electrodes placed above and below the left eye. The horizontal electrooculogram (HEOG) was recorded with electrodes placed beside the two eyes. The impedance was kept below 5 kΩ. The electrophysiological data were continuously recorded with a bandwidth 0.05–100 Hz and sampled at a rate of 1000 Hz.

Offline time-domain EEG data analysis was conducted using EEGLAB (41) and ERPLAB (42). Data were first re-referenced to linked mastoid (M1 and M2). An independent component analysis (ICA)-based artifact correction was achieved by using the ICA function of EEGLAB. Independent components with topographies representing saccades, blinks, and heart rate artifact were thus removed according to published guidelines (43). The resultant EEG data were then epoched from 200 ms pre-stimulus to 1000 ms post-stimulus and digitally low pass filtered by 30 Hz (24 dB/octave). The 200 ms pre-stimulus period was used for baseline correction. In order to remove movement artifacts, epochs were rejected when fluctuations in potential values exceeded ± 75 μV at any channels except the EOG channel. The ERPs were averaged separately for successful Stop trials and correct Go trials in each group.

Our time-frequency analysis was performed using the Matlab FieldTrip toolbox (44) and the procedures were similar to that described in a recent study (45). The filtered EEG data between 0.5–30 Hz was segmented 500 ms pre-stimulus onset to 1000 ms post-stimulus onset separately for Go and Stop trials for each group. Total event-related spectral power was obtained by transforming each epoch into the frequency domain using a sequential and overlapping unique Hanning window of 250 ms in steps of 25 ms with the multitaper time-frequency transformation (MTMCONVOL from ft_freqanalysis Fieldtrip software) method. In addition, the convolution function includes a ‘Zero’ type padding in order to cope with edging effects. After the transformation, we obtained a time-frequency spectrum with 1 Hz and 250 ms resolution. At each frequency, the results employed a dB transform [dB power = 10*log10 (power/baseline)] and were baseline corrected by subtracting the average baseline period (from − 200 to − 0 ms) from each data point. The obtained power values were then averaged over EEG epochs for trial types (i.e., Go trials and successful Stop trials) in each participant. Then, data were grand-averaged across MwoA patients and across healthy controls for each trial type.

Statistical analysis

For statistical analysis on the demographic data, a chi-square test was used to assess a between-group difference in sex ratio and independent sample t-tests were used to examine between-group differences in

age, years of education, the rate of anxiety and depression as measured by the self-rating anxiety scale (SAS) and self-rating depresson scale (SDS), and body mass index (BMI). For statistical analysis on the behavioral data, accuracy on Go trials (Go ACC) and reaction times to Go stimuli (Go RT) and the Stop signal (stop signal reaction time: SSRT) were extracted for analyses. Independent sample t-tests were used to examine between-group differences in these behavioral data.

Regarding statistical analysis on electrophysiological data, our data were analyzed according to the topographical distribution of grand averaged ERP activity as well as the methods of previous ERP studies (3, 32, 34, 46). The ERP statistical analysis involved two ERP indices of response inhibition: the stop-N2 and stop-P3. Mean amplitudes for the stop-N2 (time interval = 200–250 ms, at the C3, Cz, C4, CP3, CPz, CP4, P3, Pz, P4 electrodes) and the stop-P3 (time interval = 350–500 ms, at the FC3, FCz, FC4, C3, Cz, C4, CP3, CPz, CP4, P3, Pz, P4 electrodes) were calculated. In order to examine effects of migraine on these ERP components, we conducted a mixed analysis of variance (ANOVA), with group as a between-participants factor (patients with MwoA versus healthy controls), and trial type (Go versus Stop trials), laterality (left [C3, CP3, P3], midline [Cz, CPz, Pz], right [C4, CP4, P4] for the N2; left [FC3, C3, CP3, P3], midline [FCz, Cz, CPz, Pz], right [FC4, C4, CP4, P4] for the P3) and area (central [C3, Cz, C4], centroparietal [CP3, CPz, CP4], parietal [P3, Pz, P4] for the N2;frontocentral [FC3, FCz, FC4], central [C3, Cz, C4], centroparietal [CP3, CPz, CP4], parietal [P3, Pz, P4] for the P3) as within-participants factors. Consistent with previous findings showing that delta and theta power account for activity underlying the stop-N2 and stop-P3 components in a stop signal task (32), the same statistical analyses were conducted on event-related delta and theta power. Based on visual inspection of time-frequency plots and the methods of previous studies (45–47), the same area and laterality factors were included in such time-frequency analyses and mean power values in delta (1–4 Hz) and theta (4–8 Hz) frequency bands were extracted in the time windows used to extract mean amplitudes of the stop-N2 and stop-P3 components in order to disentangle the multiple processes underlying the stop N2–P3 complex in response inhibition.

All data were analyzed using IBM SPSS 19.0 (IBM Corp., Armonk, NY, USA). Statistical comparisons were made at p-values of $p < 0.05$, with the Greenhouse–Geisser correction when violations of sphericity occurred.

Results

Participant demographic

There were no significant difference in age, sex ratio, education years, BMI, SAS, and SDS scores between MwoA and healthy controls (Table 1).

Behavioral results

For reaction times, there was a significant effect of group on Go RT ($t(45) = -2.26$, $p < 0.05$), revealing that patiens with MwoA (448.56 ms ± 40.28) responded more slowly than healthy controls (424.19 ms ± 33.71) on Go trials. Moreover, there was also a significant effect of group on SSRT ($t(45) = -2.30$, $p <$

0.05), with SSRT being longer in patients with MwoA (303.48 ms ± 41.87) than in healthy controls (278.44 ms ± 32.65).

With regard to accuracy, there was not a significant effect of group on Go ACC ($t(45) = 1.11$, $p = 0.27$).

Electrophysiological results

N2 (200–250 ms)

The mixed ANOVA performed on the mean amplitude of the N2 revealed a significant main effect of trial type ($F(1, 45) = 383.95$, $p < 0.001$), with the N2 amplitude being larger on Stop trials than on Go trials ($p < 0.001$), athough there was not a significant main effect of group ($F(1, 45) = 1.59$, $p = 0.21$). Moreover, there was a significant interaction between group and trial type ($F(1, 45) = 6.23$, $p < 0.05$), which was due to larger amplitude of the N2 on Stop trials for patients with MwoA than for healthy controls ($p < 0.05$) (Fig. 2). There was also a significant main effect of area ($F(2,90) = 8.00$, $p < 0.005$), which was quantified by a significant interaction between area and trial type ($F(2,90) = 7.53$, $p < 0.005$). An analysis of simple effects revealed larger amplitude of the N2 in the central ($p < 0.05$) and centroparietal regions ($p < 0.005$) than in the parietal region on Stop trials, while larger amplitude of the N2 in the central region than in the centroparietal region ($p < 0.001$) on Go trials. Similarly, there was a significant main effect of laterality ($F(2,90) = 53.87$, $p < 0.001$), which was also quantified by a significant interaction with laterality and trial type ($F(2,90) = 83.26$, $p < 0.001$). An analysis of simple effects revealed larger amplitude of the N2 in the electrodes at the midline than that on the left ($p < 0.001$) and on the right ($p < 0.001$) on Stop trials and larger amplitude of the N2 in the electrodes on the right than that on the left on Stop trials ($p < 0.001$). No other significant effects were found.

P3 (350–500 ms)

The mixed ANOVA performed on the mean amplitude of the P3 revealed significant main effects of both group ($F(1, 45) = 6.26$, $p < 0.05$) and trial type ($F(1, 45) = 330.19$, $p < 0.001$), which was quantified by a significant interaction between group and trial type ($F(1, 45) = 9.74$, $p < 0.005$). An analysis of simple effects revealed larger amplitude of the P3 for patients with MwoA than for healthy controls on Stop trials ($p < 0.005$) (Fig. 2). In addition, there was a significant main effect of area ($F(3,135) = 25.74$, $p < 0.001$), which was quantified by a significant interaction between area and trial type ($F(3,135) = 32.58$, $p < 0.001$). An analysis of simple effects revealed larger amplitude of the P3 in the frontocentral ($p < 0.001$), central ($p < 0.001$) and centroparietal regions ($p < 0.001$) than in the parietal region on Stop trials, while larger amplitude of the P3 in the centroparietal region than other regions (all $p < 0.005$) on Go trials. Similarly, there was a significant main effect of laterality ($F(2,90) = 71.18$, $p < 0.001$), which was also quantified by a significant interaction with laterality and trial type ($F(3,135) = 81.03$, $p < 0.001$). An analysis of simple effects revealed larger amplitude of the P3 in the electrodes at the midline than that on the left and on the right (all $p < 0.05$) on Go trials, while larger amplitude of the P3 in the electrodes at the midline than that on the right and on the left (all $p < 0.001$) on Stop trials and larger amplitude of the P3 in the electrodes on the left than that on the right ($p < 0.001$) on Stop trials. No other significant effects were found.

Time-frequency results

200–250 ms

The mixed ANOVA performed on theta power (4 ~ 8 Hz) showed a significant main effect of trial type ($F(1, 45) = 209.03$, $p < 0.001$), with theta activity being larger on Stop trials compared to Go trials ($p < 0.001$), although there was not a significant main effect of group ($F(1, 45) = 0.05$, $p = 0.83$) and there was not a significant interaction between group and trial type ($F(1, 45) = 1.09$, $p = 0.30$). In addition, there was a significant main effect of area ($F(2,90) = 16.71$, $p < 0.001$), showing increased theta activity in the theta band in the central ($p < 0.005$) and centroparietal regions ($p < 0.001$) relative to the parietal region. Similarly, there was a significant main effect of laterality ($F(2,90) = 52.93$, $p < 0.001$), which was quantified by a significant interaction between laterality and trial type ($F(2,90) = 33.40$, $p < 0.001$). An analysis of simple effects revealed increased theta activity in the electrodes at the midline compared with that in the electrodes on the left ($p < 0.001$) and on the right ($p < 0.001$) on Go trials, while increased theta activity in the electrodes at the midline relative to that in the electrodes on the left ($p < 0.001$) and on the right ($p < 0.001$) on Stop trials and increased theta activity in the electrodes on the left compared to that in the electrodes on the right ($p < 0.001$) on Stop trials. Finally, no other significant effects were found.

The mixed ANOVA performed on delta power (1 ~ 4 Hz) showed a significant main effect of trial type ($F(1, 45) = 97.00$, $p < 0.001$), showing increased spectral power in the theta frequency band on Stop trials compared to Go trials ($p < 0.001$). However, there was not a significant main effect of group ($F(1, 45) = 0.67$, $p = 0.42$) and there was not a significant interaction between group and trial type ($F(1, 45) = 2.64$, $p = 0.11$) either. In addition, there was a significant main effect of area ($F(2,90) = 7.92$, $p < 0.005$), which was quantified by significant interaction between area and trial type ($F(2,90) = 16.28$, $p < 0.001$). An analysis of simple effects revealed increased delta activity in the electrodes in the centroparietal region compared to that in the electrodes in the central ($p < 0.001$) and parietal regions ($p < 0.05$) on Go trials, while increased delta activity in the electrodes in the central ($p < 0.05$) and centroparietal regions ($p < 0.005$) compared to that in the electrodes in the parietal region on Stop trials ($p < 0.001$). Meanwhile, there was a significant main effect of laterality ($F(2,90) = 38.35$, $p < 0.001$), which was quantified by a significant interaction between laterality and trial type ($F(2,90) = 41.69$, $p < 0.001$). An analysis of simple effects revealed increased delta activity in the electrodes at the midline compared with that in the electrodes on the left ($p < 0.01$) and on the right ($p < 0.001$) on Go trials, while increased delta activity in the electrodes at the midline relative to that in the electrodes on the left ($p < 0.001$) and on the right ($p < 0.005$) on Stop trials and increased delta activity in the electrodes on the right relative to that in the electrodes on the left ($p < 0.001$) on Stop trials. Finally, No other significant effects were found.

350–500 ms

The mixed ANOVA performed on delta power (1 ~ 4 Hz) showed a significant main effect of trial type ($F(1, 45) = 306.97$, $p < 0.001$), showing increased spectral power in the delta band on Stop trials compared to Go trials ($p < 0.001$), although there was not a significant main effect of group ($F(1, 45) = 2.57$, $p = 0.12$).

However, there was a significant interaction between group and trial type ($F(1, 45) = 9.42$, $p < 0.005$), which was due to an increase in delta activity on Stop trials for patients with MwoA compared to healthy controls ($p < 0.05$) (Fig. 3). There was also a significant main effect of area ($F(3,135) = 10.92$, $p < 0.001$), which was quantified by a significant interaction between area and trial type ($F(3,135) = 23.86$, $p < 0.001$). An analysis of simple effects revealed larger delta activity in the centroparietal region than in the central region on Go trials ($p < 0.05$), while stronger delta activity in the frontocentral ($p < 0.005$), central ($p < 0.001$) and centroparietal regions ($p < 0.001$) than in the parietal region on Stop trials. Similarly, there was a significant main effect of laterality ($F(2,90) = 35.16$, $p < 0.001$), which can also be quantified by a significant interaction with laterality and trial type ($F(2,90) = 19.64$, $p < 0.001$). The analysis of simple effects showed that delta activity reached its maximum in the electrodes at the midline compared with that on the left ($p < 0.001$) and on the right ($p < 0.001$) on Go trials, while on Stop trials, delta activity was stronger in the electrodes at the midline than that in the electrodes on the left ($p < 0.001$) and on the right ($p < 0.001$) and delta activity was larger in the electrodes on the right than that in the electrodes on the left ($p < 0.05$). Finally, No other significant effects were found.

The mixed ANOVA performed on theta power (4 ~ 8 Hz) showed a significant main effect of trial type ($F(1, 45) = 213.19$, $p < 0.001$), showing increased spectral power in the theta band on Stop trials compared to Go trials ($p < 0.001$), although there was not a significant main effect of group ($F(1, 45) = 0.23$, $p = 0.63$). Moreover, there was not a significant interaction between group and trial type ($F(1, 45) = 3.25$, $p = 0.08$). However, there was also a significant main effect of area ($F(3,135) = 32.24$, $p < 0.001$), which was quantified by a significant interaction between area and trial type ($F(3,135) = 37.21$, $p < 0.001$). An analysis of simple effects revealed stronger theta activity in the centroparietal region than in the parietal region on Go trials ($p < 0.01$), while larger theta activity in the frontocentral, central and centroparietal regions than in the parietal region on Stop trials (all, $p < 0.001$). Similarly, there was a significant main effect of laterality ($F(2,90) = 47.18$, $p < 0.001$). which can also be quantified by a significant interaction with laterality and trial type ($F(3,135) = 21.65$, $p < 0.001$). The analysis of simple effects showed theta activity reached its maximum in the electrodes at the midline compared with that in the electrodes on the left ($p < 0.001$) and on the right ($p < 0.001$) on Go trials. In contrast, on Stop trials, theta activity was stronger in the electrodes at the midline than that in the electrodes on the left ($p < 0.001$) and on the right ($p < 0.001$) and theta activity was stronger in the electrodes on the right than that in the electrodes on the left ($p < 0.001$). Finally, No other significant effects were found.

Discussion

To the best of our knowledge, the present study is the first to investigate the physiopathological basis of response inhibition during the interictal period of patients with MwoA during a stop signal task. Overall, consistent with the theory that cortical hyperexcitability is a key signature of migraine, the results in the present study revealed a decrease in suppressing prepotent responses in migraineurs which can be attributable to cortical hyperexcitability, implying the existence of dysfunctional inhibitory control at later stage of information processing.

At the behavioral level, patients with MwoA relative to healthy controls showed significantly slower RTs (SSRT) on Stop trials. However, accuracy on Go trials did not highlight any significant difference between patients with MwoA and healthy controls. Given that the stop signal reaction time (SSRT) provides an effective means of quantifying the latency of the inhibition mechanism, the slower SSRT implied a decrease or disruption in response inhibition in migraineurs. Such poorer performance during a stop signal task is in line with previous studies reporting that migraineurs during the interictal period relative to healthy controls showed significantly slower RTs on incongruent trials during the Stroop interference test without a between-group difference in commited errors (37, 48). Given that the Stroop interference test measured cognitive interference or inhibition (26), the behavioral finding in the present study indicates that the impairment in inhibitory control in migraineurs can occur not only during the early and intermediate stage of information processing, but also during the late stage of information processing, such as response execution.

At the neural level, consistent with the notion that cortical hyperexcitability is a key signature of migraine, we first found that patients with MwoA relative to healthy controls were characterized by a pronounced increase in the amplitude of the N2 in response to the stop signal in the central and parietocentral regions, but a nonsignificant between-group diference in the amplitude of the N2 in response to Go stimuli. In spite of some controversy about its functional significance, the stop-N2 is proposed to be related to premotor cognitive processes such as conflict monitoring that is involved in the initial detection of conflict between response execution and inhibition (32, 33). As a consequence, the increased stop-N2 amplitude seems to reflect a disruption of the degree of conflict monitoring that controls the concurrent and competing co-activation of response representations during early, non-motoric stages of response inhibition in patients with MwoA. Despite such findings on the amplitude of the stop-N2, there was not a difference in the topographical distribution of this ERP index of response inhibition between patients with MwoA and healthy controls. The stop-N2 reached its maximum in the central and centroparietal regions across these 2 groups. Considering source-localization studies have found that the neural generator of the stop-N2 is located around the anterior cingulate cortex (ACC) (32, 49, 50), this seems to suggest that the presence of deficient inhibitory cortical processes can be localized beyond the sensory cortical system in the migraine brain. Although our observation of the increased amplitude of the stop-N2 provides compelling evidence in support of a disruption of premotor cognitive processes such as conflict monitoring during early, non-motoric stages of response inhibition, this can not answer the question of whether the other subprocess underying response inhibition is altered. Our further analysis on the amplitude of the P3 additinoaly help with addressing this issue. Regarding the P3, we found that patients with MwoA relative to healthy controls were characterized by an increase in the amplitude of the stop-P3 in the frontocentral, central and centroparietal regions. Contrary to the stop-N2, this ERP component has been proposed to reflect late-stage inhibition of the motor system itself and cognitive evaluation of motor inhibition (32). As such, our observation of the increased amplitude of the stop-P3 in patients with MwoA indicates that patients with MwoA can also mainifest a deficit in response inhbition during the late stage of response inhibition (when inhibiting a motor response). Given that source-localization studies have also shown that the stop-P3 is mainly associated with neural activity of the primary motor cortex (M1)

and the supplementary motor areas (SMA) (32), this therefore may reflect dysfunctional activity in these cortical regions in migraineurs. Taken together, the time-domain ERP results during a stop signal task are suggestive of neurocognitive deficits while suppressing a prepotent motor response as evidenced by the increased ERP indices of response inhbitionn (stop N2–P3 complex) in patients with MwoA relative to healthy controls.

Although these two time-domain ERP indices of response inhibition greatly contribute to our understanding of how the brain detects the stop signal and decides to stop a prepotent motor response in patients with MwoA, these ERP measures can not accurately reflect the overlapping processes that need to be disaggregated in order to reflect separable mechanisms underlying response inhibition. To address this issue, the time-frequency analysis was employed in the present study to characterize event-related theta (4–8 Hz) and delta (1–4 Hz) oscillations that index two separable, but highly overlapping processes underlying the stop N2–P3 complex in response inhibition in patients with MwoA. With regard to theta and delta oscillations, the time-frequency analysis found significantly higher theta and delta activities in response to the stop signal than in response to Go stimuli in the time windows used to extract mean amplitudes of the stop-N2 and stop-P3 components, which is consistent with findings from previous studies (32, 34, 45, 46). Although both theta and delta activities in response to either the stop signal or Go stimuli in the time window used to extract mean amplitude of the stop-N2 component did not highlight any significant difference between patients with MwoA and healthy controls, patients with MwoA were associated with increased delta activity (not theta activity) relative to healthy controls in response to the stop signal rather than in response to Go stimuli in the time window used to extract mean amplitude of stop-P3 component. Despite ongoing debates on the functional significance of these two oscillatory activities (32), the relationship of TF phase dynamics to time-domain ERP measures may substantially explain the time-domain experimental effects observed in the present study. Given that previous studies have found that delta activity relative to theta activity contributed more to the stop-P3 component (32, 36), this may suggests that the increased time-domain stop-P3 observed in patients with MwoA relative to healthy controls is mainly driven by the delta activity in the same time window. In contrast to delta-related stop-P3 component, we failed to find an interaction effect between group and trial type on both theta and delta activities in the time window used to extract mean amplitude of the stop-N2. Given that theta and delta oscillations have been suggested to contribute uniquely in the opposite direction at the N2, one possible explanation may lie in the fact that their combination may lead to the non-significant interaction effect between group and trial type in the frequency domain in the time time used to extract the mean amplitude of the stop-N2.

Limitations

In spite of such promising findings, the present study still has some limitations. First, the present study included a relative small sample size, thus possibly tempering the strength of our conclusions. Going forward it is important that future research involves a larger sample size. Second, the present study only included patients suffering from migraine without aura. Given that migraine is a heterogeneous disease and the difference between migraine subtypes has been increasingly highligtened (51–53), this may

affect “generalizability” of the results in migraineurs and therefore foster future research exploring the physiopathology of response inhbition in other subforms of this disease. Third, although the stop signal task is a frequent measurement of response inhibition, there are other types of task that can be used to mesaure inhbitory control such as the Go/no-go task. Moreover, accumulating evidence has revealed differences in these measures, raising the question of whether they tap into equivalent cognitive mechanisms underlying inhbitory control capacities (54). As a consequence, future research is required to examine other measures of response inhibition to better characterize the physiopathological basis of inhbition control at later stages of information processing such as response execution. Despite these limitations, we believe that our findings are still robust and may foster further research on neuroanatomical characteristics and pathological signatures underlying inhibitory control function in migraineurs.

Conclusions

In conclusion, the present study was designed to characterize the physiopathological basis of response inhibition using event-related potentials (ERPs) in patients with MwoA during the interictal period. Our main finding is that patients with MwoA were associated with prolonged RTs to the stop signal relative to healthy controls, indicating a decrease in response inhibition in migraineurs. At the brain level, the amplitude of the stop-N2, a component of the ERPs related to conflict monitoring that is involved in the initial detection of conflict between response execution and inhibition, was significantly increased in patients with MwoA relative to healthy controls. Meanwhile, the amplitude of the stop-P3, a component of the ERPs reflecting late-stage inhibition of the motor system itself and cognitive evaluation of motor inhibition, was also significantly increased in patients with MwoA relative to healthy controls. These findings further indicate a dysfunction in ERP indices of sub-processes underlying response inhibiton in patients with MwoA, which can be attributable to cortical hyperexcitability. Moreover, time-frequency decompositions have revealed increased delta activity in the time window used to extract to the mean amplitude of the stop-P3 in patients with MwoA relative to healthy controls. Taken together, the present study offers novel insights into how the brain detects the stop signal and decides to stop a prepotent motor response in migraineurs and provides both behavioral and neural evidence showing the existence of dysfunctional inhibitory control at later stage of information processing in migraineurs. These findings not only aid in a growing body of literature showing the presence of a deficit inhbition control in migraineurs, but also may have important implications for further research charactering inhibitory control alterations in migraineurs.

Abbreviations

MwoA: migraine without aura; SST:Stop signal task; ERPs:Event-related potentials; SSRT:Stop signal reaction time

Declarations

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Chinese PLA General Hospital and informed written consent was obtained for all participants.

Consent for publication

Written informed consent for publication was obtained.

Availability of data and materials

The datasets used and analyzed during the present study are available from the corresponding authors on reasonable request.

Competing interests

The authors declare that they have no competing interests.

Funding

This work was supported by the National Natural Science Foundation of China (Grant No. 81671077, 81600952, 81771180, 81771200, 81901134 and 81901145 to S.Y.), Beijing Natural Science Foundation Essential Research Project (Grant No. Z170002 to S.Y.), The National Natural Science Foundation of China (Grant No. 31600929 to Y.L.), The Fundamental Research Funds for the Central Universities (010914380002 to Y.L.).

Authors contributions

G.C.,Y.L. and S.Y. conceived and designed the study; G.C., D.Z., R.W. and S.Y. collected the data. G.C. analyzed the data under the supervision of Y.L.; G.C. and Y.L. wrote and edited the draft manuscript; S.Y. commented on the manuscript. I.O. provided diligent proofreading of this manuscript. All authors approved the final manuscript.

Acknowledgements

The authors wish to thank the volunteers involved in this study.

References

1. Arnold M (2018) Headache classification committee of the international headache society (IHS) the international classification of headache disorders. Cephalalgia 38(1):1–211

2. Pietrobon D, Moskowitz MA (2013) Pathophysiology of migraine. Annu Rev Physiol 75:365–391
3. Burch RC, Loder S, Loder E, Smitherman TA. The Prevalence and Burden of Migraine and Severe Headache in the U nited S tates: Updated Statistics From Government Health Surveillance Studies. Headache: The Journal of Head and Face Pain. 2015;55(1):21–34
4. Stovner LJ, Andree C (2010) Prevalence of headache in Europe: a review for the Eurolight project. J Headache Pain 11(4):289
5. Yu S, Liu R, Zhao G, Yang X, Qiao X, Feng J et al (2012) The Prevalence and Burden of Primary Headaches in China: A Population-Based Door-to-Door Survey. Headache: The Journal of Head Face Pain 52(4):582–591
6. Wang X, Zhou H, Sun J, Xing Y, Zhu Y, Zhao Y (2016) The prevalence of migraine in university students: A systematic review and meta-analysis. European journal of neurology 23(3):464–475
7. Lantéri-Minet M, Duru G, Mudge M, Cottrell S (2011) Quality of life impairment, disability and economic burden associated with chronic daily headache, focusing on chronic migraine with or without medication overuse: a systematic review. Cephalalgia 31(7):837–850
8. Luo N, Qi W, Tong W, Tan F, Zhang Q, He J et al (2014) Prevalence and burden of headache disorders in two neighboring provinces of China. Journal of Clinical Neuroscience 21(10):1750–1754
9. May A, Schulte LH (2016) Chronic migraine: risk factors, mechanisms and treatment. Nature Reviews Neurology 12(8):455
10. Vecchia D, Pietrobon D (2012) Migraine: a disorder of brain excitatory–inhibitory balance? Trends in neurosciences 35(8):507–520
11. Bashir A, Lipton RB, Ashina S, Ashina M (2013) Migraine and structural changes in the brain: a systematic review and meta-analysis. Neurology 81(14):1260–1268
12. Marucco E, Lisicki M, Magis D (2019) Electrophysiological Characteristics of the Migraine Brain: Current Knowledge and Perspectives. Curr Med Chem 26(34):6222–6235
13. Pietrobon D, Striessnig J (2003) Neurobiology of migraine. Nat Rev Neurosci 4(5):386–398
14. Coppola G, Di Lorenzo C, Parisi V, Lisicki M, Serrao M, Pierelli F (2019) Clinical neurophysiology of migraine with aura. J Headache Pain 20(1):42-
15. Bhaskar S, Saeidi K, Borhani P, Amiri H (2013) Recent progress in migraine pathophysiology: role of cortical spreading depression and magnetic resonance imaging. Eur J Neurosci 38(11):3540–3551
16. de Tommaso M, Ambrosini A, Brighina F, Coppola G, Perrotta A, Pierelli F et al (2014) Altered processing of sensory stimuli in patients with migraine. Nature Reviews Neurology 10(3):144–155
17. Coppola G, Pierelli F, Schoenen J (2007) Is the cerebral cortex hyperexcitable or hyperresponsive in migraine? Cephalalgia 27(12):1427–1439
18. Coppola G, Parisi V, Di Lorenzo C, Serrao M, Magis D, Schoenen J et al (2013) Lateral inhibition in visual cortex of migraine patients between attacks. J Headache Pain 14(1):20-
19. Palmer JE, Chronicle EP, Rolan P, Mulleners WM (2000) Cortical Hyperexcitability is Cortical Under-Inhibition: Evidence From a Novel Functional Test of Migraine Patients. Cephalalgia 20(6):525–532

20. Goadsby PJ, Holland PR, Martins-Oliveira M, Hoffmann J, Schankin C, Akerman S (2017) Pathophysiology of Migraine: A Disorder of Sensory Processing. Physiol Rev 97(2):553–622
21. Coppola G, Schoenen J (2012) Cortical Excitability in Chronic Migraine. Curr Pain Headache Rep 16(1):93–100
22. Haigh SM, Chamanzar A, Grover P, Behrmann M (2019) Cortical Hyper-Excitability in Migraine in Response to Chromatic Patterns. Headache: The Journal of Head Face Pain 59(10):1773–1787
23. Akdeniz G, Gumusyayla S, Vural G, Bektas H, Deniz O (2020) Changes in face and face pareidolia processing in patients with migraine: an ERP study. J Neurophysiol 123(3):876–884
24. Aurora S, Ahmad B, Welch K, Bhardhwaj P, Ramadan N (1998) Transcranial magnetic stimulation confirms hyperexcitability of occipital cortex in migraine. Neurology 50(4):1111–1114
25. Jurado MB, Rosselli M (2007) The Elusive Nature of Executive Functions: A Review of our Current Understanding. Neuropsychol Rev 17(3):213–233
26. Hung Y, Gaillard SL, Yarmak P, Arsalidou M (2018) Dissociations of cognitive inhibition, response inhibition, and emotional interference: Voxelwise ALE meta-analyses of fMRI studies. Hum Brain Mapp 39(10):4065–4082
27. Verbruggen F, Logan GD (2008) Response inhibition in the stop-signal paradigm. Trends Cogn Sci 12(11):418–424
28. Verbruggen F, Aron AR, Band GP, Beste C, Bissett PG, Brockett AT et al (2019) A consensus guide to capturing the ability to inhibit actions and impulsive behaviors in the stop-signal task. Elife 8:e46323
29. Luck SJ, Mathalon DH, O'Donnell BF, Hämäläinen MS, Spencer KM, Javitt DC et al (2011) A roadmap for the development and validation of event-related potential biomarkers in schizophrenia research. Biol Psychiatry 70(1):28–34
30. Houston RJ, Schlienz NJ (2018) Event-related potentials as biomarkers of behavior change mechanisms in substance use disorder treatment. Biological Psychiatry: Cognitive Neuroscience Neuroimaging 3(1):30–40
31. Horvath A, Szucs A, Csukly G, Sakovics A, Stefanics G, Kamondi A (2018) EEG and ERP biomarkers of Alzheimer's disease: a critical review. Frontiers in bioscience (Landmark edition) 23:183–220
32. Huster RJ, Enriquez-Geppert S, Lavallee CF, Falkenstein M, Herrmann CS (2013) Electroencephalography of response inhibition tasks: functional networks and cognitive contributions. Int J Psychophysiol 87(3):217–233
33. Dimoska A, Johnstone SJ, Barry RJ (2006) The auditory-evoked N2 and P3 components in the stop-signal task: indices of inhibition, response-conflict or error-detection? Brain Cogn 62(2):98–112
34. Band GP, van Boxtel GJ (1999) Inhibitory motor control in stop paradigms: review and reinterpretation of neural mechanisms. Acta Psychol (Amst) 101(2–3):179–211
35. Waller DA, Hazeltine E, Wessel JR. Common neural processes during action-stopping and infrequent stimulus detection: The frontocentral P3 as an index of generic motor inhibition. International Journal of Psychophysiology. 2019

36. Harper J, Malone SM, Bernat EM (2014) Theta and delta band activity explain N2 and P3 ERP component activity in a go/no-go task. Clin Neurophysiol 125(1):124–132
37. Annovazzi P, Colombo B, Bernasconi L, Schiatti E, Comi G, Leocani L (2004) Cortical function abnormalities in migraine: neurophysiological and neuropsychological evidence from reaction times and event-related potentials to the Stroop Test. Neurol Sci 25(3):s285–s28s7
38. Raz S, Koren A, Levin C (2019) Attention, response inhibition and brain event-related potential alterations in adults with beta-thalassaemia major. Br J Haematol 186(4):580–591
39. Chen G, Zhang L, Ding W, Zhou R, Xu P, Lu S et al (2015) Event-related brain potential correlates of prospective memory in symptomatically remitted male patients with schizophrenia. Frontiers in Behavioral Neuroscience 9:262
40. Chen G, Ding W, Zhang L, Cui H, Jiang Z, Li Y (2017) Neurophysiological Evidence of Compensatory Brain Mechanisms Underlying Attentional-Related Processes in Symptomatically Remitted Patients with Schizophrenia. Frontiers in psychology 8:550
41. Delorme A, Makeig S (2004) EEGLAB: an open source toolbox for analysis of single-trial EEG dynamics including independent component analysis. J Neurosci Methods 134(1):9–21
42. Lopez-Calderon J, Luck SJ (2014) ERPLAB: an open-source toolbox for the analysis of event-related potentials. Front Hum Neurosci 8:213
43. Jung T-P, Makeig S, Westerfield M, Townsend J, Courchesne E, Sejnowski TJ (2000) Removal of eye activity artifacts from visual event-related potentials in normal and clinical subjects. Clin Neurophysiol 111(10):1745–1758
44. Oostenveld R, Fries P, Maris E, Schoffelen J-M FieldTrip: open source software for advanced analysis of MEG, EEG, and invasive electrophysiological data. Computational intelligence and neuroscience. 2011;2011
45. Andreu CI, Palacios I, Moënne-Loccoz C, López V, Franken IH, Cosmelli D et al (2019) Enhanced response inhibition and reduced midfrontal theta activity in experienced Vipassana meditators. Scientific reports 9(1):1–11
46. González-Villar AJ, Bonilla FM, Carrillo-de-la-Peña MT (2016) When the brain simulates stopping: Neural activity recorded during real and imagined stop-signal tasks. Cognitive Affective Behavioral Neuroscience 16(5):825–835
47. Messerotti Benvenuti S, Buodo G, Palomba D (2017) Appetitive and aversive motivation in dysphoria: A time-domain and time-frequency study of response inhibition. Biol Psychol 125:12–27
48. Schytz HW, Ciftçi K, Akin A, Ashina M, Bolay H (2010) Intact neurovascular coupling during executive function in migraine without aura: interictal near-infrared spectroscopy study. Cephalalgia 30(4):457–466
49. Botvinick MM, Cohen JD, Carter CS (2004) Conflict monitoring and anterior cingulate cortex: an update. Trends Cogn Sci 8(12):539–546
50. Nieuwenhuis S, Yeung N, van den Wildenberg W, Ridderinkhof KR (2003) Electrophysiological correlates of anterior cingulate function in a go/no-go task: effects of response conflict and trial type

frequency. Cogn Affect Behav Neurosci 3(1):17–26

51. Kincses ZT, Veréb D, Faragó P, Tóth E, Kocsis K, Kincses B et al. Are Migraine With and Without Aura Really Different Entities? Frontiers in Neurology. 2019;10(982)
52. Lipton RB, Bigal ME (2005) Migraine: epidemiology, impact, and risk factors for progression. Headache 45(Suppl 1):S3–Ss13
53. Hansen JM, Charles A (2019) Differences in treatment response between migraine with aura and migraine without aura: lessons from clinical practice and RCTs. J Headache Pain 20(1):96
54. Littman R, Takács Á (2017) Do all inhibitions act alike? A study of go/no-go and stop-signal paradigms. PLOS ONE 12(10):e0186774

Figures

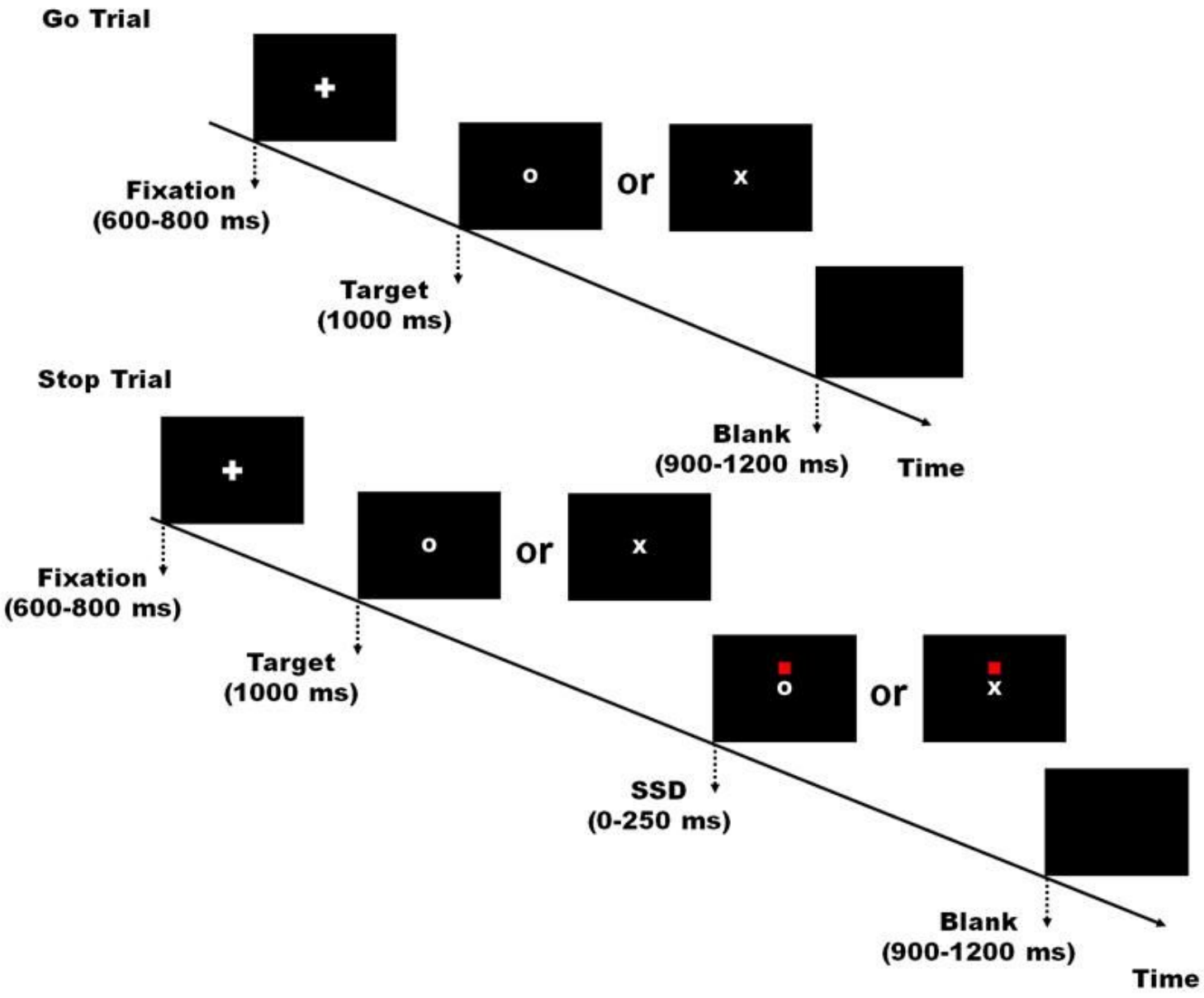

Figure 1

Stop signal paradigm. This task included 80% Go trials and 20% Stop trials. On Go trials, participants were presented with a fixation cross on a black computer screen lasting for 600-800 ms, which is immediately followed by a Go stimulus (the letter 'X' or 'O') (a Go signal) lasting for 1000 ms. Participants were instructed to judge the shape of the Go stimulus as accurately and quickly as possible via a button press with the index fingers of the left and right hands. On the remaining Stop trials (20%), the stop stimulus (a red square appearing above the location of the go stimulus) appeared after the Go stimulus after a variable delay of 0-250 ms in a step of 50 ms (the stop signal delay; SSD), cuing participants to withhold their responses to the Go stimulus. A variable intertrial interval was 1500-2000 ms.

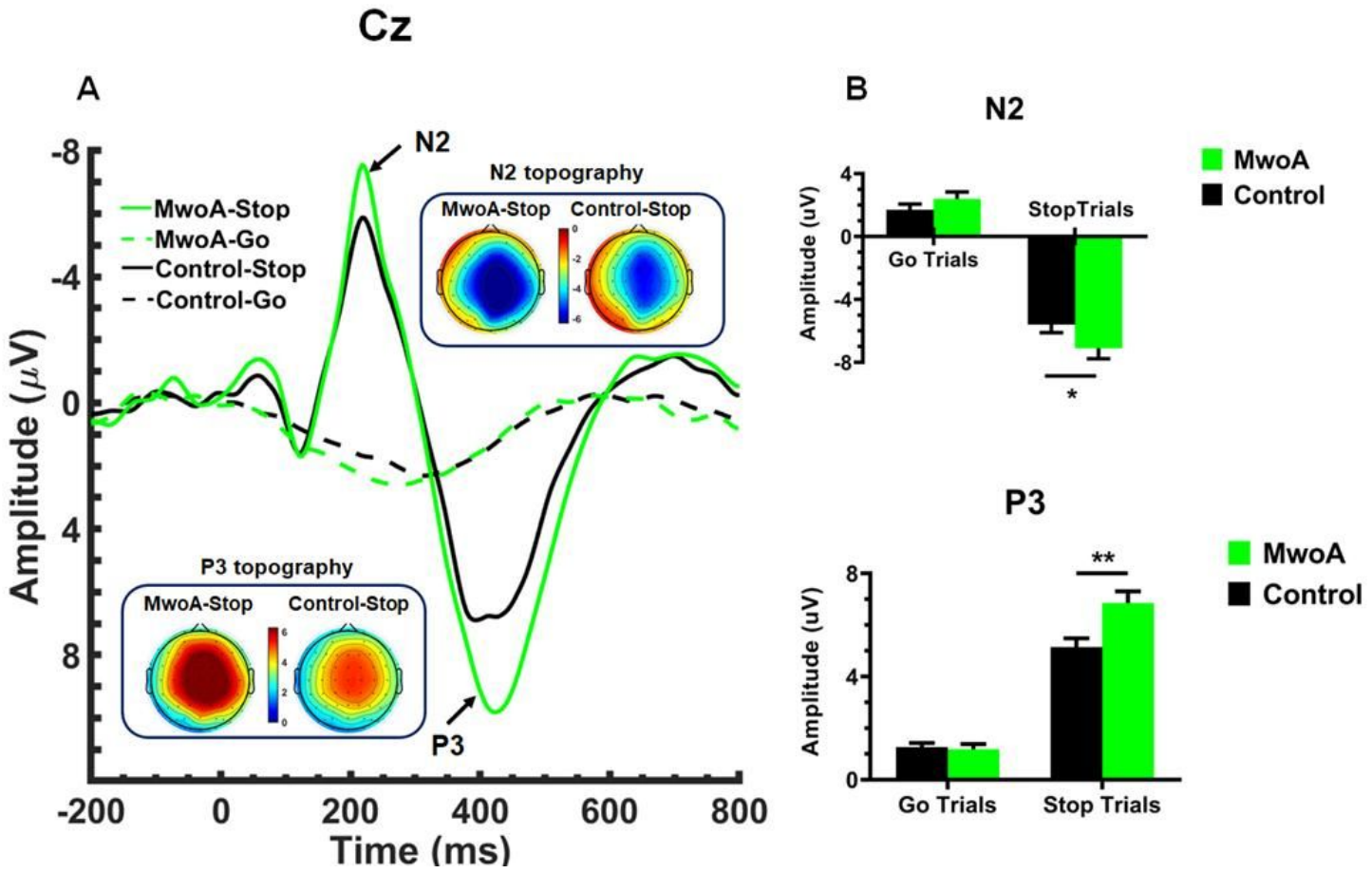

Figure 2

Time-domain ERPs results. (A) Grand average ERP waveforms recorded at Cz evoked by Go signals (dashed lines) and successful Stop signals (solid lines), and the topography of the N2 (200-250 ms) and P3 (350-500 ms) in patients with MwoA and healthy controls. (B) Means and standard errors (SEs) of the amplitudes of the N2 and P3 in the two groups. *denotes $p<0.05$ and **denotes $p < 0.01$.

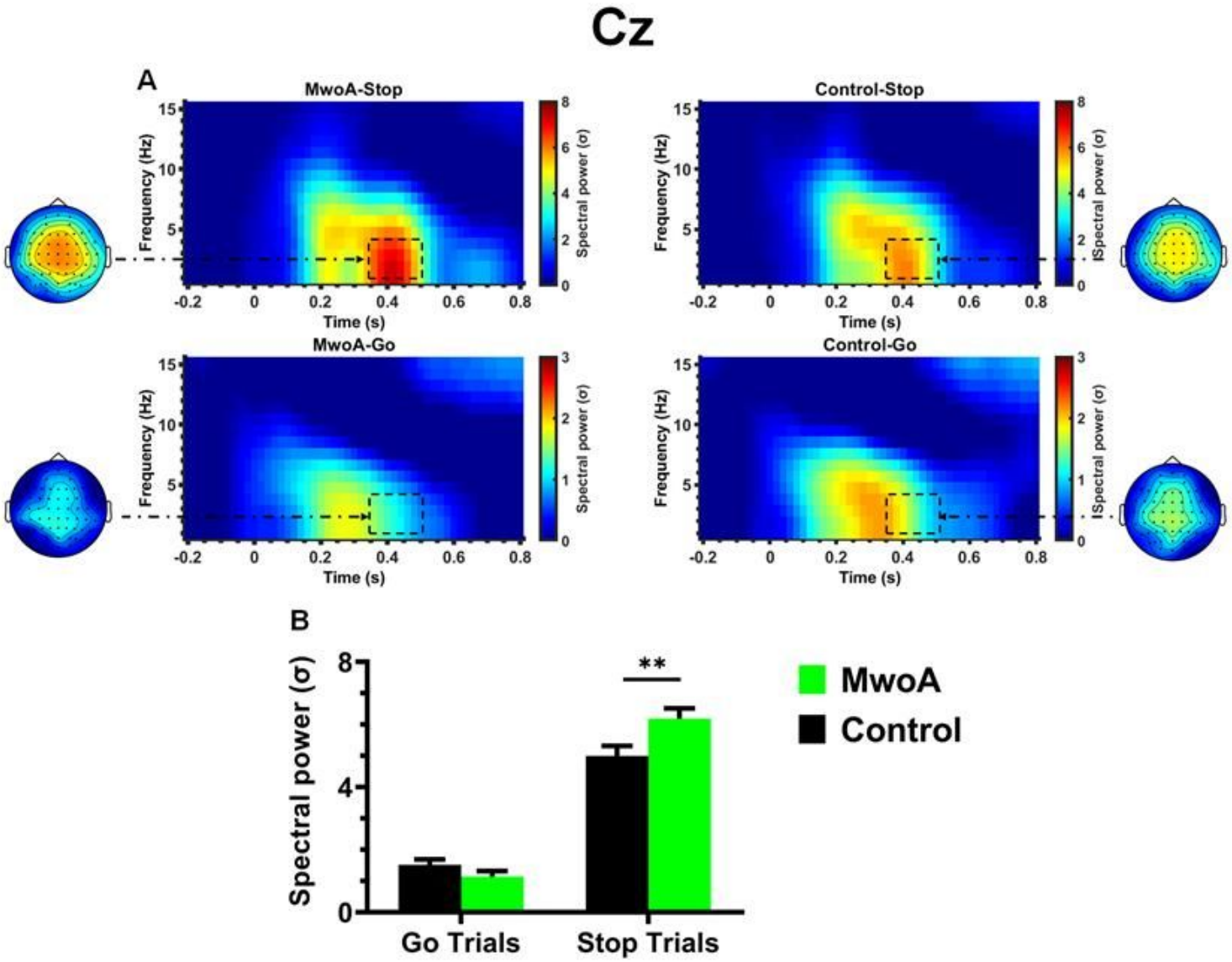

Figure 3

Time-frequency results. (A) Time-frequency plots showing delta changes in normalized power in go and stop trials (left) for patients with MwoA and healthy controls for the selected electrode (Cz). Black dotted squares indicate the time-frequency region in which theta power in stop trials was significantly higher in patients with MwoA than in healthy controls. Scalp topography maps show the spatial distribution of theta power (4–8 Hz) in go and stop trials between 350–500 ms. The color scale indicates spectral power in SD. (B) Means and standard errors (SEs) of the delta power (4–8 Hz) between 350–500 ms at Cz in the two groups. **, $p < 0.01$.