Individual-specific effects of transcranial electrical stimulation on 40-Hz auditory steady-state responses

Aurimas Mockevičius, Xiaojuan Wang, Jovana Bjekić, Saša R. Filipović, Inga Griškova-Bulanova

***Abstract*— Although transcranial electrical stimulation (tES) has shown positive behavioral outcomes in neuropsychiatric disorders, evidence has been mixed thus far. Therefore, the possibility of tracking brain activity changes following tES via neurophysiological markers would benefit a better understanding of tES effects and the future development of tES protocols. One promising marker is the auditory steady-state response (ASSR), an externally controlled oscillatory brain activity, typically at 40 Hz, evoked by a periodic auditory stimulus. In the present study, we aimed to test the offline effects of different types of tES on 40-Hz ASSR. Participants underwent four conditions of tES which was applied over the left posterior parietal cortex: transcranial direct current (tDCS), transcranial alternating current (tACS), oscillatory transcranial direct current (otDCS) and sham stimulation. Individually determined theta frequency was delivered in the tACS and otDCS protocols. Immediately following the tES application, electroencephalogram (EEG) was recorded during 40-Hz auditory click stimulation. The analysis of time-frequency data from 29 participants showed that phase-locking and amplitude of 40-Hz ASSR did not differ among tES conditions. However, baseline ASSR (during sham stimulation) had a significant negative correlation with change in ASSR relative to sham (tES – sham) as well as a positive correlation with the magnitude of change (|tES – sham|) following each tES protocol. The results suggest that tES effects on 40-Hz ASSR may be individual-specific and likely depend on the baseline neuronal state. The findings encourage future research to focus on individual factors that may contribute to tES outcomes.**

***Index Terms*— auditory steady-state response, EEG, transcranial alternating current stimulation, transcranial electrical stimulation, transcranial direct current stimulation**

I. INTRODUCTION

NEURAL oscillations represent synchronized patterns of brain activity which play a pivotal role in the transmission and integration of information across brain networks [1]. Specifically, oscillatory activity at the gamma frequency range (> 30 Hz) reflect bottom-up sensory and cognitive information processing [2], [3]. Given their importance, methods aiming to reliably assess synchronized gamma oscillations are being investigated, which include auditory steady-state responses (ASSR) [4].

ASSR is a continuous synchronized activity entrained by rhythmic auditory stimulus and characterized by stability in amplitude and phase. Primarily, it reflects activity in the auditory cortex and the related neural pathways [4], [5]. Although generated within the auditory system, ASSR spreads beyond the auditory cortex [6], [7] and can be detected with the electroencephalogram (EEG) over a wide scalp area predominantly in the frontocentral region [8]. It has been shown that auditory steady-state stimulation at around 40 Hz produces the strongest and most stable ASSR [9]. As a result, 40-Hz ASSR is considered a robust way to evaluate the generation and maintenance of oscillatory gamma activity.

ASSR is proposed as a neurophysiological marker of excitatory-inhibitory (E/I) balance [10], [11]. Cortical E/I balance represents the ratio between the activity of excitatory and inhibitory cells within neural circuits, which contributes to the integrity and excitability of the system [12], [13]. Evidence suggests that neuropsychiatric disorders characterized by aberrant E/I balance, such as schizophrenia [14], depression [15] or autism spectrum disorder [13], also exhibit deficits in gamma ASSR [10], [16], [17], [18].

In recent years, advancements have been made in the application of noninvasive brain stimulation in neuropsychiatric disorders [19]. In particular, transcranial electrical stimulation (tES) has received considerable attention due to its safety and the ease of application [20]. TES is based on a low intensity electrical current applied over the scalp with the aim to improve brain function. Various types of tES, including transcranial direct current stimulation (tDCS), transcranial alternating current stimulation (tACS) and oscillatory transcranial direct current stimulation (otDCS) are

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thought to exert different modulatory effects on cortical excitability. In particular, tDCS modulates the resting membrane potential by applying a constant current between two opposing electrodes, thereby increasing cortical excitability [21]. TACS entrains neural oscillations to the stimulation frequency by rhythmically altering the polarity of the electrodes [22]. Meanwhile, otDCS combines features of tDCS and tACS, with the current oscillating at a specific frequency while maintaining the polarity of electrodes. This approach is thought to induce changes in both cortical excitability and oscillatory brain activity [23].

Importantly, it has been proposed that tES effects can be explained by changes in the E/I balance [24], [25]. Considering that both tES action and the generation of ASSR may involve similar neurophysiological mechanisms, ASSR modulation via tES could provide significant insights into the network-level outcomes of tES. Previous studies have attempted to modulate gamma ASSR using tES (for review, see [26]). Generally, the application of tDCS [27], [28], [29], [30], [31] and tACS delivered at theta [32], [33], alpha [29], [33], [34], [35], [36] or gamma [30], [32], [36], [37], [38], [39] frequencies have yielded mixed results, with a number of studies also reporting no significant changes in gamma ASSR after tES. It is likely that differences in experimental designs [26] and substantial individual variability [24] contributed to inconsistent findings in previous studies. In addition, no attempts have been made to explore otDCS as a means to modulate ASSR. For these reasons, more research is needed to clarify the influence of various extrinsic and intrinsic factors on the neuromodulatory effects of tES on ASSR.

The present study aimed to systematically investigate the effect of different tES types on ASSR to test whether ASSR could reflect tES-induced network-level changes. Specifically, we comparatively assessed the effects of anodal tDCS, theta-tACS, and theta-otDCS on phase locking and evoked amplitudes of 40-Hz ASSR. We sought to clarify if the effects vary between different types of tES and whether they depend on the baseline characteristics of ASSR at the individual level.

II. Methods

A. Study design

The data were collected from a sham-controlled, randomized cross-over experiment conducted as part of the larger MEMORYST study (for a detailed description, see [40]). During four experimental sessions carried out on separate days, participants received continuous electrical stimulation while performing cognitive tasks. Each tES session involved a different stimulation condition presented in a counterbalanced order: tDCS, otDCS, tACS, and sham. Immediately following tES, 5 min resting-state EEG activity was acquired, after which click-based periodic auditory stimulation was delivered during an EEG recording.

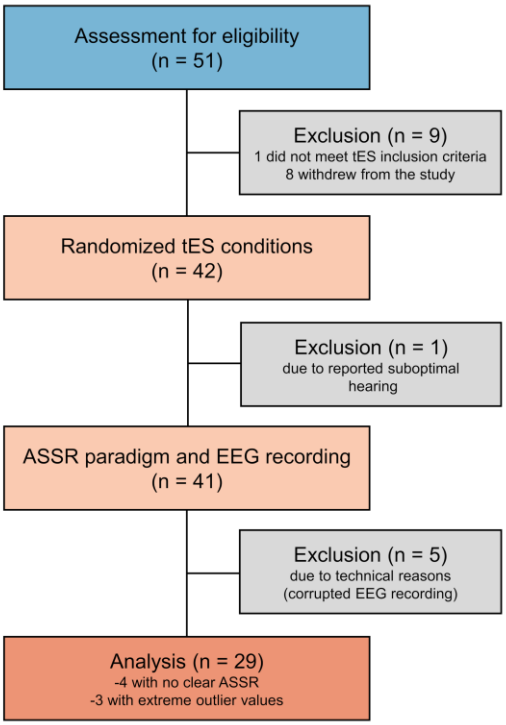

Fig. 1. CONSORT flow chart of participant exclusion.

B. Participants

A group of healthy young adults participated in the study and all satisfied the inclusion criteria for tES application [40]. To determine the sample size, a priori power analysis for planned statistical analysis in a within-subject design was conducted for the theoretically defined medium effect size i.e. Cohen $|d|= 0.50$ [41]. The analysis showed that 42 participants were sufficient to detect $|d| \geq 0.50$ with a power of 0.90. The participants were enrolled on a rolling basis until the desired sample size was met. The CONSORT flow chart provides a complete overview of participants' inclusion/exclusion (Figure 1). After the initial eligibility assessment, 42 participants completed all four tES sessions, and the ASSR paradigm was administered to 41; data of 5 participants were not analyzed due to technical reasons (missing, corrupted or interrupted EEG recording), resulting in data of 36 participants used in the analysis. Additional 7 subjects were excluded during the analysis (4 showing no clear ASSR and 3 with outlier values), resulting in the final sample of 29 participants (M_{age} = 25.13, SD_{age} = 3.93; 17 F) used for statistical evaluation. Therefore, the achieved power to detect $|d| = 0.50$ was 0.75; $|d| = 0.61$ will be detected with the power of 0.80, and $|d| \geq 0.61$ with the power of 0.90. The study was conducted in line with the guidelines of the Declaration of Helsinki and was approved by the Institutional Ethics Board (EO129/2020). Written informed consent was obtained from all participants, and all were compensated for their participation.

C. Transcranial Electrical Stimulation and EEG acquisition

A mobile, battery-operated, hybrid tDCS-EEG Starstim device (Neuroelectrics Inc., Barcelona, Spain) was used for both EEG acquisition and tES. The device was attached to the back of the neoprene cap and was remotely operated via Neuroelectrics® Instrument Controller (NIC) software (Neuroelectrics Inc., Barcelona, Spain).

Two round rubber electrodes (25 cm2) inserted in saline-soaked sponge pockets were used for stimulation. Stimulation electrodes were placed at P3 and the contralateral cheek (return). In each stimulation condition, the protocol lasted 20 minutes in total. TACS was delivered as 2 mA peak-to-peak (i.e., between −1 mA and +1 mA) sinusoidal oscillating current at individual theta frequency (ITF, 4–8 Hz). The method used for ITF extraction is described in detail in [42]. The otDCS was delivered in positive polarity (i.e., anodal current) with the current oscillating at ±0.5 mA in sinusoidal mode around +1.5 mA (i.e., between +1 mA and +2 mA), also at ITF. Anodal tDCS had a constant current intensity of +1.5 mA. All active stimulation protocols had a gradual ramp up/down of 30 s at the beginning and at the end of the stimulation period. Finally, in sham condition, the current was briefly delivered for 60 s at the beginning and at the end of the stimulation period (double ramp up/down sham protocol), both with a gradual ramp up to 1.5 mA (30 s) and immediate gradual ramp down (30 s). During tES, participants performed cognitive tasks to keep them engaged and create uniform conditions for each participant across all tES conditions.

The EEG signals were recorded with a sampling rate of 500 Hz, 0–125 Hz (DC coupled) bandwidth, and 24 bits—0.05 µV resolution. Gel Ag/AgCl electrodes (4 mm diameter, 1 cm2 gel-contact area) were placed according to the international 10-10 EEG system at Fp1, Fp2, Fz, F3, F4, F7, F8, T7, T8, Cz, C3, C4, CP5, CP6, Pz, P4, PO7, PO8 and Oz positions. The 19-electrode set-up was selected to avoid contact with the stimulating electrode (P3) while maintaining reasonable whole-head coverage. Depending on the quality of the signal, either the dual CMS-DRL ear clip electrode attached to the right earlobe, or two pre-gelled sticktrodes - the CMS on the right mastoid, and the DRL just below - were used.

D. Auditory Stimulation

40-Hz click-based auditory stimulus was designed in the MATLAB environment and presented binaurally through earphones with a sound pressure level adjusted to 60 dB. Each stimulus lasted 500 ms and consisted of 20 white noise clicks of 1.5 ms duration which were separated by silent periods of 25 ms, corresponding to 40 Hz. The stimulus was presented 100 times with an inter-stimulus interval set at 750 ms, resulting in an overall duration of approximately 2 minutes. Subjects were instructed to sit comfortably and listen to the sounds while looking at a fixation point on the screen in front of them.

E. EEG Data Processing

Data preprocessing was performed in the Matlab environment using the EEGlab package [43]. Data was filtered by applying a 1-Hz highpass filter and notch filter (48-52 Hz) to remove line noise. Bad channels were manually rejected and reconstructed using spline interpolation after which channels were re-referenced to average. Independent component analysis (ICA) was performed using default EEGlab settings. Components related to eye blinks were removed. Next, data was epoched at -500 ms to 1100 ms relative to the stimulus onset, and epochs containing substantial noise or artifacts were manually removed.

Fieldtrip package [44] was used for data analysis. Morlet wavelet (10 cycles) time-frequency decomposition was performed in the frequency range of 30-50 Hz in 1 Hz step in the time window from -500 ms to 1100 ms. Phase information was extracted to calculate the Phase Locking Index (PLI, phase consistency over epochs). To compute evoked amplitude (EA, amplitude of the evoked activity), the time series of the signals were averaged over epochs and Morlet wavelet decomposition with the same parameters was performed on the averaged signal. Amplitude information was obtained and relative baseline normalization was applied to PLI and EA data by dividing the values at each time point by the average in the baseline period (-400 to 0 ms). PLI and EA values were averaged in the time window between 200 ms and 500 ms post-stimulus onset, in the frequency range of 40±2 Hz and over channels in three frontocentral regions separately – left (F3, C3), midline (Fz, Cz) and right (F4, C4).

F. Statistical Evaluation

Statistical analysis was carried out using R programming language. Prior to the statistical evaluation, a visual inspection of time-frequency plots was performed to ensure the inclusion of only those participants who showed clear ASSR in the sham condition. Extreme outliers were identified using boxplots and participant-data with values above Q3 + 3×IQR or below Q1 – 3×IQR in at least one of the measures were excluded from further analysis.

First, to assess the effects of different tES techniques on 40-Hz ASSR, mean PLI and EA were compared in the left (F3, C3), midline (Fz, Cz), and right (F4, C4) frontocentral regions separately among sham, tDCS, otDCS and tACS conditions using repeated-measures ANOVA. Simple planned contrasts between the sham and each of the active tES conditions (i.e. tDCS, tACS, otDCS), were calculated separately for each measure and ROI.

Second, we wanted to assess if tES effects are dependent on individual differences in baseline ASSR. Thus, we calculated the change in PLI and EA after the tES application relative to the response level in the sham condition. Here, the ASSR in the sham condition was used as a proxy of baseline / ordinary brain response. Two measures were computed: the simple difference (tES – sham) and the absolute difference (|tES – sham|). Simple difference shows the direction and the amount of change in PLI and EA following the stimulation (i.e. increase or decrease), while the absolute difference highlights the magnitude of the change regardless of the direction. Pearson correlations between the baseline PLI and EA (during sham condition) and the change in PLI and EA measures after each tES condition were estimated separately in the left, center, and right regions.

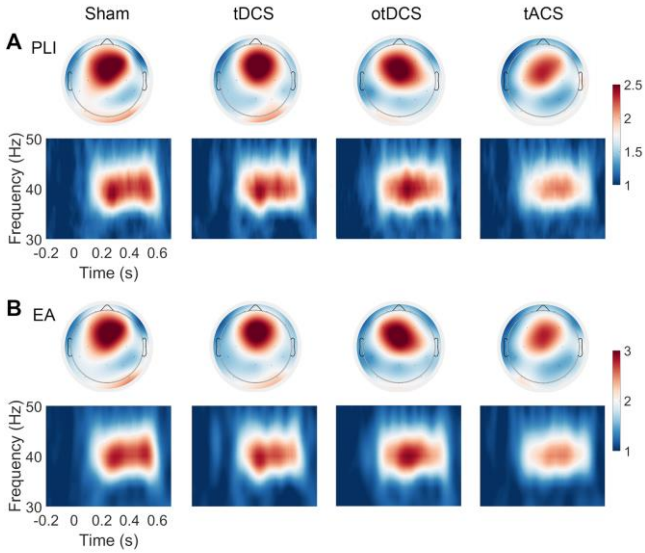

Fig. 2. PLI (A) and EA (B) grand-average plots. Top row – topographies with average response in each channel in the time window of 200-500 ms and frequency window of 40±2 Hz; Bottom row – time-frequency plots with responses averaged over the 6 frontocentral channels (F3, Fz, F4, C3, Cz, C4) for visualization purpose. Responses in each condition (sham, tDCS, otDCS, and tACS) are presented in separate columns. Green rectangles in A depict the analyzed regions (left, midline, right).

TABLE I
DESCRIPTIVE STATISTICS AND ANOVA RESULTS OF PLI AND EA IN EACH ROI AND CONDITION

	PLI			EA		
	Left	Midline	Right	Left	Midline	Right
	Descriptive Statistics (M ± SD)					
Sham	2.04 ± 0.59	2.50 ± 0.66	2.07 ± 0.59	2.34 ± 0.79	2.99 ± 0.90	2.39 ± 0.90
tDCS	1.85 ± 0.71	2.54 ± 0.90	2.13 ± 0.72	2.14 ± 0.98	2.99 ± 1.13	2.40 ± 0.81
otDCS	2.04 ± 0.59	2.47 ± 0.77	2.06 ± 0.63	2.35 ± 0.82	2.98 ± 1.06	2.35 ± 0.84
tACS	1.85 ± 0.68	2.22 ± 0.71	1.86 ± 0.58	2.09 ± 0.83	2.64 ± 0.93	2.12 ± 0.76
	ANOVA					
	F(3,84) = 1.49	F(3,84) = 1.38	F(3,84) = 1.32	F(3,84) = 1.31	F(3,84) = 1.21	F(3,84) = 0.96
	p = 0.22	P = 0.26	p = 0.26	p = 0.28	p = 0.31	p = 0.41

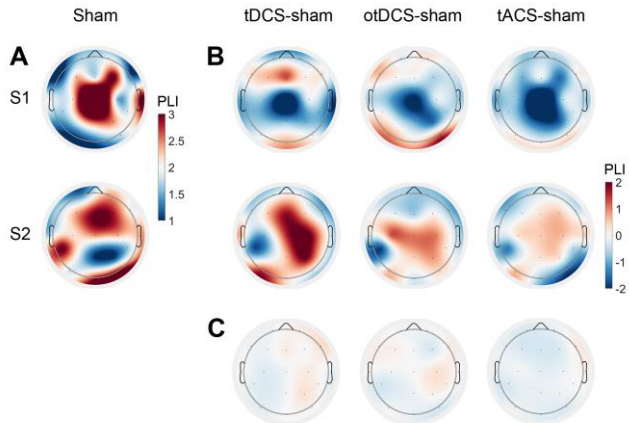

Fig. 3. A-B. Single-subject topography plots of PLI in sham condition (A) and PLI simple difference (tES – sham) in each tES condition (B). Examples of ASSRs from participants who showed decreased PLI (S1) and increased PLI (S2) after tES are presented. C. Grand average topography plots of PLI contrast (tES – sham) in each tES condition for two subjects.

III. RESULTS

Grand average time-frequency plots and topographies depicting baseline-corrected PLI and EA are presented in Figure 2. A clear increase in PLI and EA is present during the auditory stimulation at the stimulation frequency (40 Hz) and the response is localized in the frontocentral area. Comparisons between conditions were performed in the left (F3, C3), midline (Fz, Cz), and right (F4, C4) ROIs separately, after averaging responses in two corresponding channels. No significant main effects of stimulation condition were observed in PLI and EA in any of the ROIs. Descriptive statistics and ANOVA results are presented in Table 1.

PLI and EA simple differences between each tES condition and sham condition were computed. On average, the change in PLI after each tES condition in the whole frontocentral area was close to 0 (tDCS, M = -0.03, SD = 0.56; otDCS, M = -0.01, SD = 0.57; tACS, M = -0.23, SD = 0.57). Similar results were present in EA simple difference (tDCS, M = -0.06, SD = 0.73; otDCS, M = -0.01, SD = 0.82; tACS, M = -0.29, SD = 0.79). However, a closer look revealed high inter-individual variability in effects with pronounced changes in both directions, which resulted in a net near zero change at the group level. Namely, looking at the individual-level simple differences between tES conditions, we observed 15/29 participants showing an increased PLI in the tDCS condition, 14/29 in the otDCS condition, and 14/29 in the tACS condition. PLI simple difference values among subjects ranged from -1.23 to 0.89 for tDCS, from -1.31 to 0.84 for otDCS, and from -1.46 to 0.57 for tACS. Examples of participants that showed decreased (subject 1) and increased (subject 2) PLI relative to the sham condition following tES and grand average simple differences are shown in Figure 3. A similar pattern was observed for EA, with 13/29 subjects exhibiting increased EA in tDCS condition, 17/29 in otDCS, and 14/29 in tACS. Individual EA simple differences ranged from -1.75 to 1.52 for tDCS, from -1.79 to 1.39 for otDCS, and from -2.04 to 1.07 for tACS.

Evaluation of ASSR changes as a function of baseline physiological responsiveness revealed significant correlations between parameters of the ASSR in sham conditions and the change in response after tES. Generally, ASSR measures (both PLI and EA) in the absence of stimulation were negatively correlated with the simple difference in ASSR measures following active tES relative to sham, while the absolute difference showed a positive correlation with ASSR measures from the sham stimulation condition (see Figure 4 for illustration). Correlation coefficients and p values are presented in Table 2.

IV. DISCUSSION

Low-intensity tES techniques have shown great promise for inducing neurophysiological and behavioral changes in healthy brain [45], [46] as well as in neuropsychiatric disorders [47], [48]. Nonetheless, tES literature faces reproducibility challenges due to a high variability in tES-responsiveness [49], [50]. This is why systematically investigating the effects of tES, especially at the neurophysiological level, is essential in order to gain a better understanding of tES mechanisms of action on the network level. To this end, extensive research is being conducted on various EEG/MEG measures to map out the neuromodulatory effects of

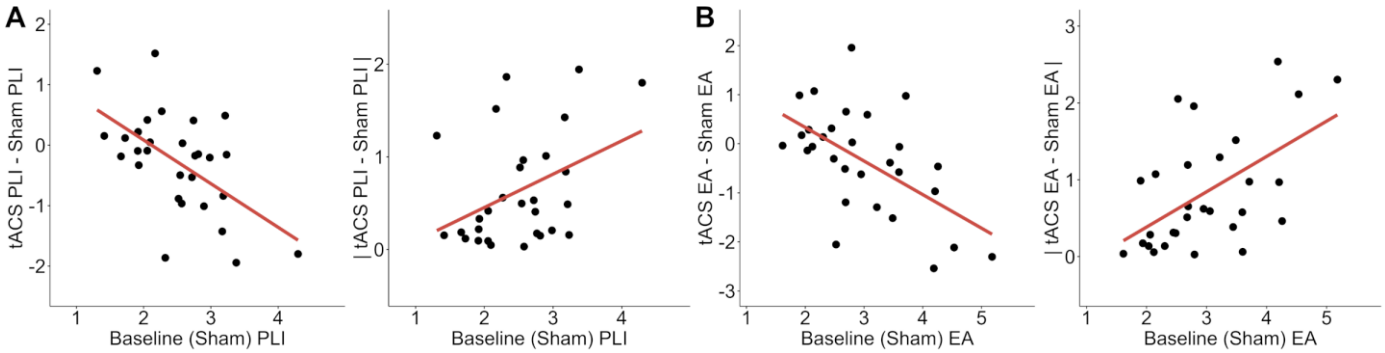

Fig. 4. Correlations between baseline (sham) response and the response change in tACS relative to sham condition in the midline frontocentral area (Fz, Cz) for PLI (A) and EA (B). Left column – correlation between sham response and the simple difference between tACS and sham (tACS - sham), right column – correlation between sham response and the absolute change in response after tACS relative to sham (|tACS - sham|).

TABLE II
CORRELATIONS BETWEEN BASELINE RESPONSE AND RESPONSE CHANGE

	PLI			EA		
	Left	Midline	Right	Left	Midline	Right
			tES – sham			
tDCS	**r = -0.39***	**r = -0.47***	r = -0.34	r = -0.31	**r = -0.41***	**r = -0.46***
otDCS	**r = -0.53****	**r = -0.50****	**r = -0.60****	r = -0.29	**r = -0.46***	**r = -0.60****
tACS	**r = -0.50****	**r = -0.57****	**r = -0.68****	**r = -0.49****	**r = -0.58****	**r = -0.66****
			| tES – sham |			
tDCS	**r = 0.45***	**r = 0.43***	r = 0.02	**r = 0.47***	**r = 0.52****	r = 0.31
otDCS	r = -0.27	**r = 0.56****	r = 0.25	r = 0.26	**r = 0.44***	**r = 0.41***
tACS	r = 0.10	**r = 0.40***	**r = 0.46***	**r = 0.38***	**r = 0.58****	**r = 0.46***

* $p < 0.05$
** $p < 0.01$

tES [51]. The possibility of tracking changes in the standardized neurophysiological markers during or after tES is highly beneficial in this regard. One category of such measures is the steady-state responses, characterized by a stable, externally controlled oscillatory brain activity evoked by rhythmic visual, auditory, or somatosensory stimuli. In particular, ASSRs evoked by periodic auditory stimuli offer the opportunity to probe the brain's ability to generate synchronous activity in the gamma (>30 Hz) frequency range [4], which is of particular importance due to its role in sensory and cognitive information processing [2]. In addition, ASSRs provide a unique experimental model of stable cortical electrophysiological activity [52] which is not subjected to unpredictable random variations typical for transient responses and event-related potentials [52], [53].

Building on this, our study applied different tES protocols (tDCS, otDCS, tACS) to monitor changes in ASSR magnitude and phase synchronization, aiming to assess their potential as markers of tES neuromodulatory effects. We expected that given the different mechanisms of action, these techniques could have differential effects on ASSR. Yet, the results revealed no significant differences in ASSR measures between tES protocols and the sham condition. However, the data exhibited high inter-individual variability of the effects and significant correlations were found between baseline ASSR (in sham condition) and the change in ASSR relative to sham after each tES protocol. Specifically, both PLI and EA simple differences between tES and sham (tES – sham) correlated negatively with the baseline ASSR outcomes, while the absolute level of change (|tES - sham|) displayed a significant positive relationship, with the most consistent results obtained in the midline frontocentral electrodes.

Previous studies reported different tES effects on gamma-range ASSRs. With regards to tDCS, both increased [27] and reduced [28] ASSR was reported, although other studies showed no changes [29], [30], [31]. Research utilizing tACS generally showed an inhibitory effect of alpha-band tACS on ASSR [33], [34], [35], [36]; however, in one study, ASSR was enhanced following alpha-tACS in schizophrenia patients [29]. Conversely, an increase in gamma-range ASSR was shown after application of tACS at the same gamma frequency as during periodic auditory stimulation in both healthy participants [30], [37] and dyslexia patients [38], [39]. Yet, other studies reported no such effects [32], [36]. So far, only two studies investigated ASSR after theta-tACS, showing either no effects [33] or reduced ASSR [32].

The divergent findings in tES/ASSR studies could be partially explained by considerable variability in tES parameters. Some studies targeted specific brain areas, including temporal [30], [32], [33], [35], [36], [38], [39], frontal [27], [31] and central [28] areas, whereas others applied tES over multiple regions [29], [34], [37]. Considering that ASSR is generated primarily in the auditory cortex, it might have a different sensitivity to tES depending on how far the stimulated area is from the main source of ASSR. In addition to the targeted brain areas, tES/ASSR studies are also characterized by high variability in tES parameters. For example, 1) duration, ranging from 2 to 20 min in total; 2) current intensity, ranging from 1 to 2 mA, with some studies also using individually-determined intensity [32], [37]; and 3) the frequency of tACS, with frequencies either fixed across the sample and/or chosen individually for each participant [34], [37]. It is likely that certain combinations of these settings would result in different tES effects on ASSR, leading to inconsistencies in the reported results.

Besides the technical characteristics of tES, intrinsic factors related to brain activity per se may increase the complexity of tES effects. Variables such as age, gender, and anatomical and physiological features of the nervous system may act as confounders, contributing to individual differences in tES outcomes [24], [49], [50]. In particular, large inter-individual

variability exists in the cortical excitation and inhibition (E/I) balance which determines the integrity and the excitability of neural circuits [12], [13]. Accordingly, it is proposed that tES may have different effects, depending on individual-specific E/I balance [24]. For example, individuals with a more excitable state may benefit less from anodal tDCS than those with lower excitability in the stimulated area [49]. Studies also indicate that participants may be divided into groups of tES "responders" and "non-responders" due to individual features of the stimulated brain area [49], [54]. Therefore, it is possible that in the studies showing no changes in ASSR following tES, the effect could have varied between individuals, similarly to the present work.

In our study, no effects of tDCS, theta-otDCS or theta-tACS on ASSR were observed at the group level. This is not surprising given that research generally shows inconsistent effects of tES on various electrophysiological parameters [55]. However, significant correlations between ASSR in the sham condition and the change in ASSR following real tES were observed. Subjects who were more responsive to periodic auditory stimulation at the baseline had a more pronounced inhibitory effect of tES (regardless of tES type) on 40-Hz ASSR, which is in line with the findings of ASSR reduction following theta-tACS [32]. In addition, [27] showed a similar negative correlation between baseline ASSR and the change in the response after tDCS. However, contrary to our findings, this study also reported a group-level increase in ASSR following tDCS, and the increase was stronger in participants who had a weaker baseline ASSR. The discrepancies between the results in [27] and our study could be explained by network-activity-dependent effects [56] and the differences in stimulated areas. Firstly, in our study, subjects were engaged in online cognitive tasks, whereas in [27] tDCS was delivered during the resting-state. Secondly, in the latter work, tDCS electrodes were placed over the frontal cortex, while in our study, anodal tDCS was delivered over the left posterior parietal cortex. Thus, based on network-activity dependence of tES effects [56], it is likely that neural activity related to cognitive task execution was modulated by tDCS in our experiment, which may have subsequently interfered with the generation of ASSR, but only in subjects characterized by a stronger baseline response. On the contrary, resting-state tDCS delivered in [27] potentially induced a baseline increase in the excitability in the frontal cortex, which is implicated in ASSR generation [6], [7], leading to the facilitation of the response.

Despite the described differences between our work and [27], both studies provide evidence that tES effects on 40-Hz ASSR may be individual-specific and likely depend on the state of the neural system. Gamma activity arises from the interplay between glutamatergic pyramidal neurons and inhibitory GABAergic interneurons, with their balance modulating the oscillation amplitude and frequency [57]. Accordingly, ASSR is considered as a marker of the E/I balance [10], [11]. Given that both tES effects and ASSR generation depend on individual-specific E/I balance, the response to periodic auditory stimulation has potential to be used as a marker of tES-related brain activity changes as well as a predictor of individual response to tES. However, our findings are correlational in nature and provide only preliminary evidence. Systematic research is still needed to determine the impact of extrinsic factors and individual differences on the modulatory effects of tES on gamma ASSR.

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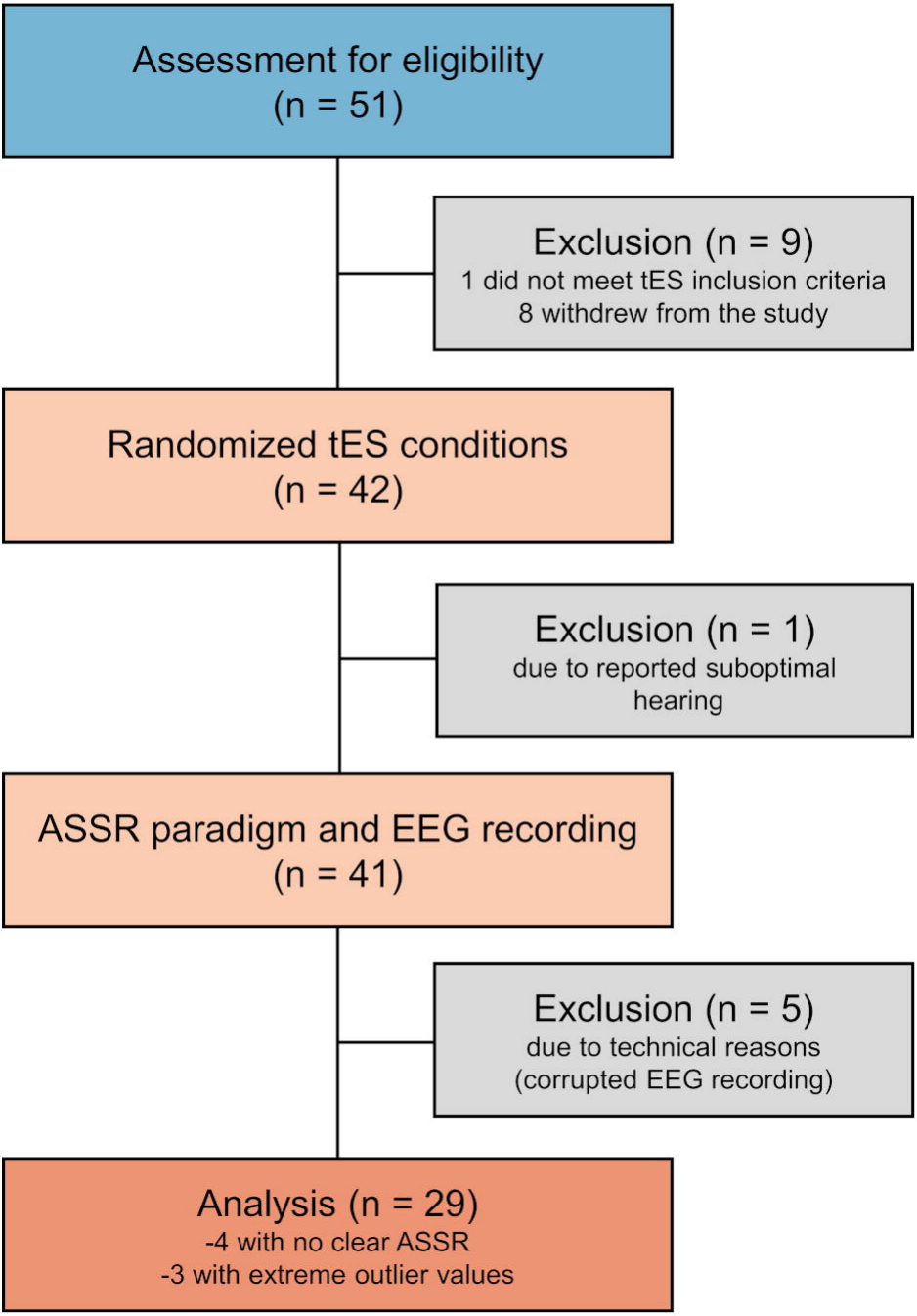
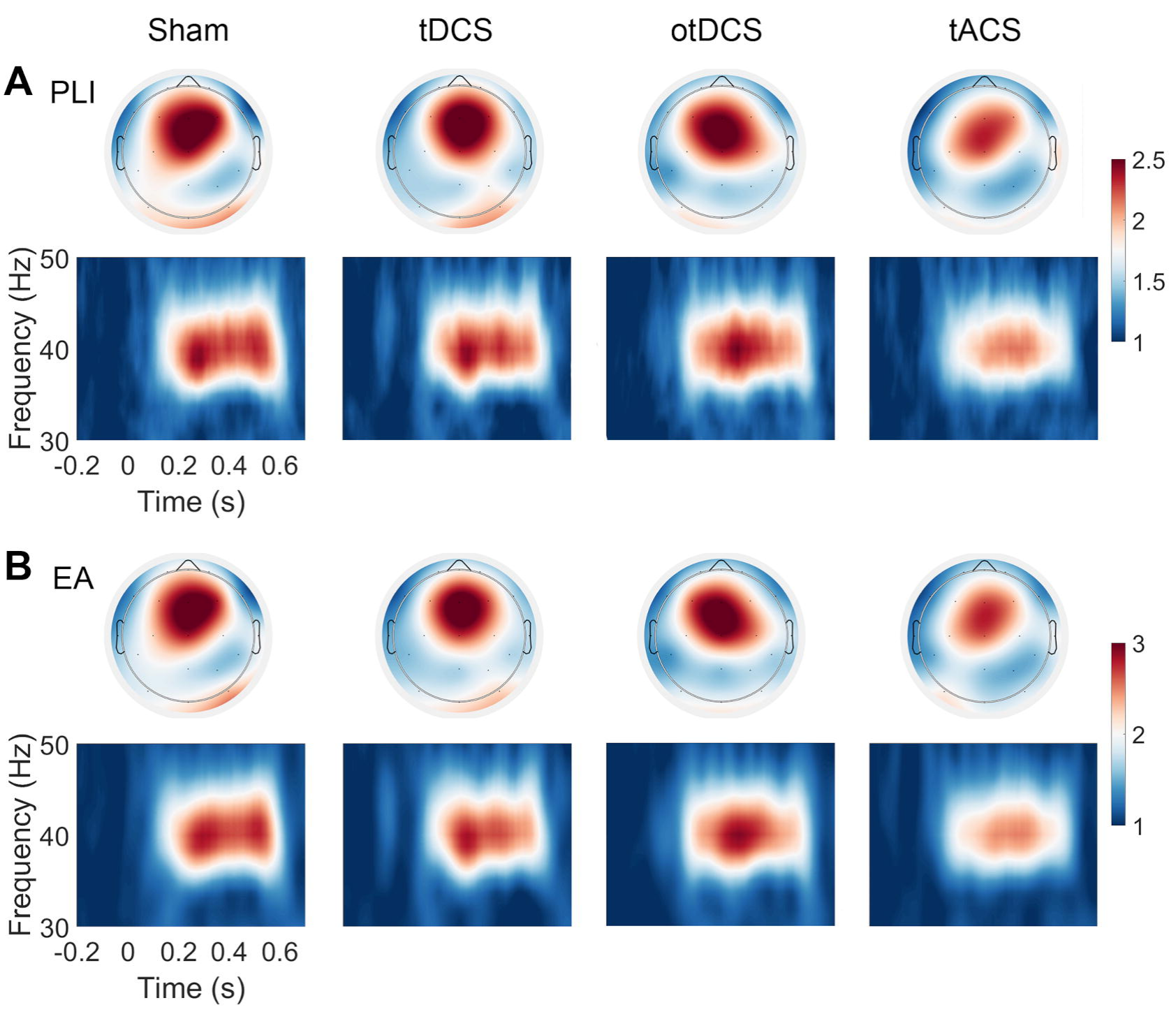

Assessment for eligibility
(n = 51)
Exclusion (n = 9)
1 did not meet tES inclusion criteria
8 withdrew from the study
Randomized tES conditions
(n = 42)
Exclusion (n = 1)
due to reported suboptimal hearing
ASSR paradigm and EEG recording
(n = 41)
Exclusion (n = 5)
due to technical reasons
(corrupted EEG recording)
Analysis (n = 29)
-4 with no clear ASSR
-3 with extreme outlier values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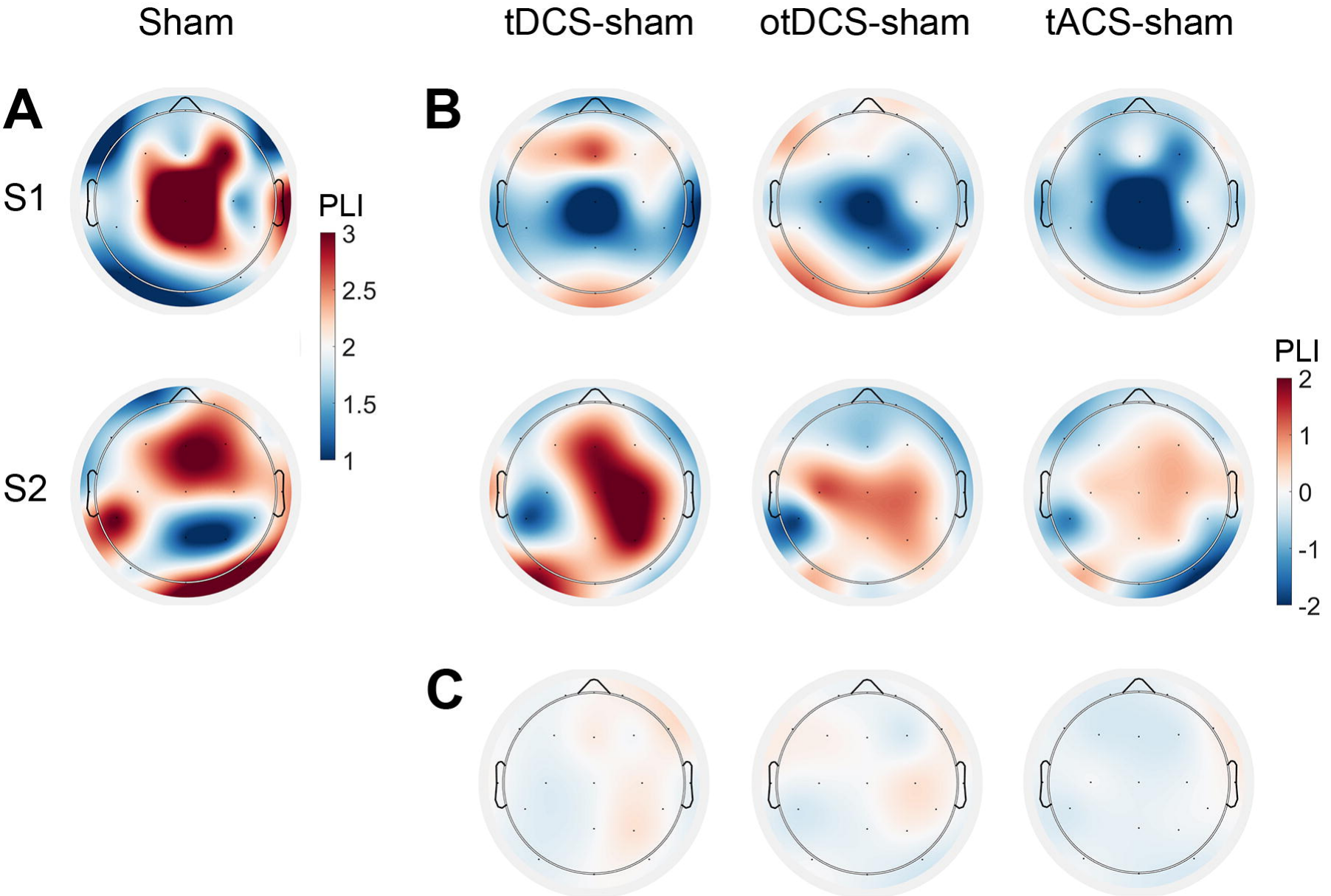
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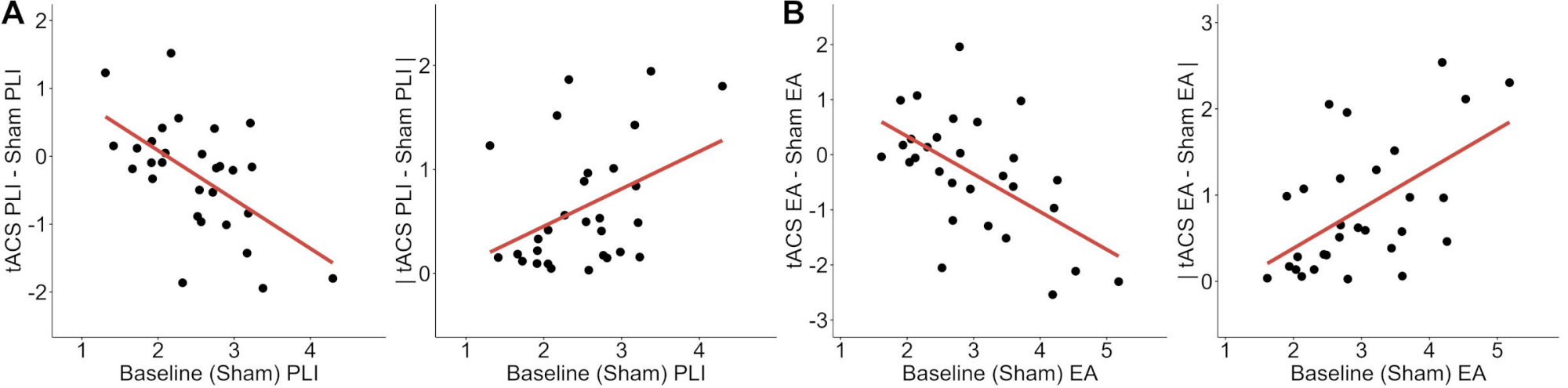
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