Received: 26 May 2021 | Revised: 22 November 2021 | Accepted: 29 November 2021

DOI: 10.1111/ejn.15563

RESEARCH REPORT

EJN European Journal of Neuroscience FENS WILEY

Modulating verbal working memory with fronto-parietal transcranial electric stimulation at theta frequency: Does it work?

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Funding information
Deutsche Forschungsgemeinschaft, Grant/Award Number: SA 1872/2-2

Edited by: Gregor Thut

Abstract

Oscillatory theta activity in a fronto-parietal network has been associated with working memory (WM) processes and may be directly related to WM performance. In their seminal study, Polanía et al. (2012) (de-)coupled a fronto-parietal theta-network by applying transcranial alternating current stimulation (tACS), and showed that anti-phase tACS led to slower and in-phase tACS to faster response times in a verbal WM task compared to placebo stimulation. In the literature, this 'synchronization-desynchronization' effect has only been partly replicated, and electric field modelling suggests that it might not be the fronto-parietal network that is primarily stimulated during in-phase tACS with a shared return electrode. This provides one possible reason for inconsistency in the literature. In this study, we aimed to reproduce the findings reported by Polanía et al. (2012). We also aimed to investigate whether in-phase theta tACS with multiple close-by return electrodes for focal stimulation of the frontal and the parietal cortex will have at least as much of a facilitatory effect as the in-phase stimulation as indicated by Polania et al. (2012). In a single-trial distributional analysis, we explored whether mean, variation and right-skewness of the response time distribution are affected. Against our hypothesis, we found no 'synchronization-desynchronization' effect by fronto-parietal theta tACS on response times using the same delayed letter discrimination task and stimulation parameters in two experiments, both between-subjects and within-subjects. However, we could show that in a more demanding 3-back task, fronto-parietal in-phase and in-phase focal theta tACS substantially improved task performance compared to placebo stimulation.

KEYWORDS
connectivity, fronto-parietal network, theta oscillations, transcranial alternating current stimulation (tACS), working memory

1 | INTRODUCTION

The transient storage of information and flexible usage of this stored information is known as working memory (Baddeley, 2012; Cowan, 2008). There is compelling evidence that activity in a network comprising frontal and parietal cortical regions—called the fronto-parietal working memory network—can be considered as neural signature of working memory processes (D'Esposito & Postle, 2015; Ptak et al., 2017). Synchronous rhythmical activity at theta frequency in this fronto-parietal network, particularly, has been discussed to be associated with working memory processes (Cooper et al., 2015; Sauseng et al., 2005, 2010), and may be directly related to working memory performance (Polanía et al., 2012).

In their seminal study, Polanía et al. (2012) tried modulating fronto-parietal theta-activity and as a consequence impact on verbal working memory performance. In an initial EEG experiment, they had observed increased fronto-parietal phase synchronization in the theta range and that response times were reduced when the phase lag was close to 0°. The authors then used transcranial alternating current stimulation (tACS) at 6 Hz over left prefrontal and parietal cortices either with 0° or 180° phase difference. I.e., the fronto-parietal network was stimulated either in-phase (0°) or anti-phase (180°). Thus, the fronto-parietal network was supposed to be coupled or decoupled, respectively. Polanía et al. (2012) provided evidence that in-phase fronto-parietal theta tACS led to increased working memory performance (faster response times) compared to a placebo stimulation, whereas anti-phase stimulation had detrimental effects on working memory performance (slower response times).

This effect of a phase-dependent modulation of task performance, the so-called 'synchronization-desynchronization effect', has triggered research on the functional relevance of long-range neuronal coupling. Since then several studies have been published where the authors actively manipulated band-specific coherence within a cortical network using tACS (e.g., Alagapan et al., 2019; Alekseichuk et al., 2017; Helfrich et al., 2014; Kleinert et al., 2017; Polanía et al., 2015; Strüber et al., 2014; van Schouwenburg et al., 2017; Violante et al., 2017). Within the domain of working memory, Violante et al. (2017) were able to partly reproduce the results by Polanía et al. (2012) in one experiment, showing an improvement of working memory performance during in-phase fronto-parietal theta tACS. In another experiment combining tACS and fMRI, which of course is difficult to compare with the original one due to a lower number of trials and the noisier environment of an MRI scanner, no effect of stimulation on behaviour could be detected (Violante et al., 2017). Kleinert et al. (2017), however, could not find any significant difference in working memory performance between in-phase and anti-phase fronto-parietal tACS at theta frequency. One reason why there might be inconsistency in attempts to reproduce the findings by Polanía et al. (2012) could be the way the frontal and parietal stimulation electrodes had been referenced. Saturnino et al. (2017) estimated electrical field distribution for different previously published dual-site tACS montages. They could show that using one shared return electrode (e.g., over electrode position Cz) for two stimulation electrodes over frontal and parietal sites in the in-phase stimulation condition led to the strongest stimulation effect under the return electrode. This means that the time varying electrical current patterns from this in-phase stimulation are spatially less confined to the cortical target sites compared to those from the anti-phase stimulation which works without a third reference electrode, such that the conditions do not only differ in their phase relationships. Recently, this was corroborated experimentally using in vivo recordings in nonhuman primates (Alekseichuk et al., 2019). Therefore, Saturnino et al. (2017) proposed in-phase focal stimulation over frontal and parietal cortex where multiple close-by return electrodes can be used to focally stimulate the frontal and the parietal cortex, respectively. This focally induced activity could then be delivered with a 0° phase lag, that is, in-phase, truly synchronously driving a fronto- parietal theta network and only differing in the relative phase of the applied currents. Similar electrode configurations were used by van Schouwenburg et al. (2017), who used three right-lateralized central reference electrodes located in-between the stimulation electrodes over the fronto-parietal locations, or by Helfrich et al. (2014) who surrounded bilateral parietal stimulation electrodes with four surrounding reference electrodes each. As an alternative to surrounding the stimulation electrodes with multiple close-by return electrodes, centre-surround ring montages can similarly achieve a better control of current distribution (Bortoletto et al., 2016; Saturnino et al., 2017).

This study aimed to reproduce the findings reported by Polanía et al. (2012). Thus, we hypothesized that compared to placebo stimulation, 0° phase difference (in-phase stimulation) leads to faster response times and 180° phase difference (anti-phase stimulation) would lead to slower response times in a verbal working memory task. Further, we aimed to investigate whether focal fronto-parietal in-phase theta tACS, where the stimulation electrodes are surrounded by multiple close-by return electrodes as suggested by Saturnino et al. (2017), would have at least as much of an facilitatory effect as

the in-phase stimulation suggested by Polanía et al. (2012). Based on electric field modelling, the focal stimulation would be supposed to truly and more specifically impact on the fronto-parietal network. Therefore, we expected that focal in-phase fronto-parietal theta tACS should produce an at least as large reduction in response times in a verbal working memory task compared to placebo stimulation as fronto-parietal in-phase stimulation with a single common return electrode. We investigated these research questions both in a between-subjects experiment, in which participants received one type of stimulation during a single session, and in a within-subjects experiment, in which participants received all types of stimulation in separate sessions. In both experiments, we measured their working memory performance in the same delayed letter recognition task as used by Polanía et al. (2012) and in the within-subjects experiment, we additionally measured their working memory performance in a more difficult 3-back task.

2 | EXPERIMENT 1: BETWEEN-SUBJECTS EXPERIMENT

2.1 | Pre-registration of study protocols

This experiment was pre-registered on Open Science Framework (https://osf.io/4z7wk/).

2.2 | A priori power analysis

A-priori power analysis for determining sample size for the current experiment was performed with G*Power software (3.1.9.4, Faul et al., 2007). Effect sizes, if not indicated initially in the existing literature, were calculated from the reported statistical indices (Lakens, 2013). Demonstrating a significant effect of fronto-parietal theta tACS on working memory performance, Polanía et al. (2012) reported an effect size of $f = .718$ in their second experiment and Violante et al. (2017) obtained an effect of $f = .923$ in their first experiment. Kleinert et al. (2017) did not find any significant effect on working memory performance, nor did Violante et al. (2017) in their second experiment. However, in the latter two experiments, an exact effect size could not be reconstructed from the reported statistical estimates. Therefore, as a rather conservative effect size estimate for the current experiment, we took a third of the mean of the effect sizes reported by Polanía et al. (2012) in experiment 2, and Violante et al. (2017; exp. 1) resulting in $f = .2735$. Using this estimate of effect size, a significance level of $\alpha = .05$ and a power of $1 - \beta = .80$, power analysis for a mixed 4 (stimulation group) × 2 (test phase) ANOVA suggested a minimal sample size of 44 participants (11 per stimulation group), each being tested twice within the experimental session—during a baseline without stimulation and again during stimulation.

2.3 | Participants

We tested 48 typically developed volunteers in experiment 1. Participants were recruited by opportunity sampling mainly within the student community of the Ludwig-Maximilians-University Munich, Germany. Inclusion criteria as described in Antal et al. (2017) were applied and the age-range for inclusion was defined as 18 to 40 years. Two participants had to be excluded due to technical issues or being older than the pre-defined age. Thus, the remaining sample consisted of 46 participants (28 female, 18 male, 0 diverse) with a mean age of 21.33 years (SD = 3, range: 19–33 years). Forty-one of them were right handed, 4 left handed and 1 ambidextrous, as assessed by the Edinburgh Handedness Inventory (Oldfield, 1971). All gave written informed consent prior to their participation and received course credits upon completion. The study was approved by the local Ethics Review Board and conducted according to the Declaration of Helsinki.

2.4 | Task and stimuli

Participants performed the same delayed letter recognition task (see Figure 1) as used by Polanía et al. (2012). Three sample letters ('L', 'T' and 'C') were briefly presented (350 ms) in randomized order and masked for another 1000 ms. Then, a numerical cue indicated whether to remember the first, second or third of the previously presented letters. After a 1500 ms delay interval a probe letter was shown, and participants were asked to indicate as quickly and correctly as possible whether the probe letter matched the letter held in memory. The probe was always one of the three previously presented letters and was displayed until a response was registered, but maximally for 2000 ms. Participants responded by pressing one of two buttons with their index finger or middle finger of the right hand to indicate a match or non-match, respectively. Each experimental block consisted of 90 trials with all possible stimulus sequences balanced and randomized in order. Before the start of the proper experiment, participants practiced the task on 18 trials.

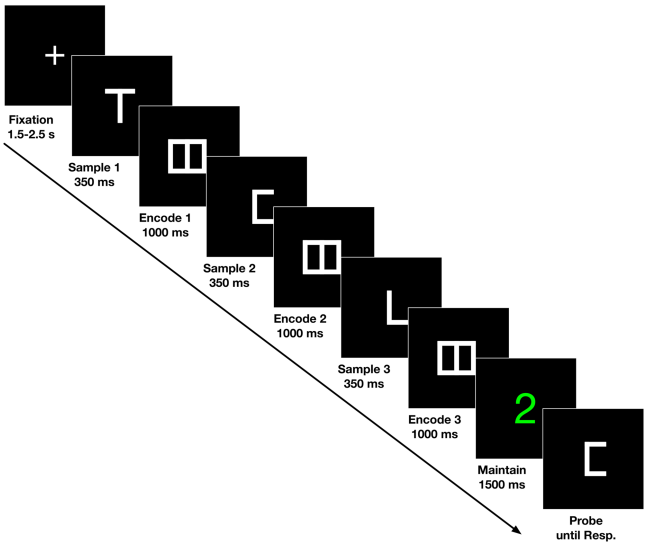

FIGURE 1 Exemplary trial sequence of the task in experiment 1. The task was the same as in Polanía et al. (2012). After three letters were encoded, a numerical cue indicated whether the first, second or third encoded letter should be maintained. The task was to indicate whether the following probe letter matched with the maintained letter or not. This example shows a match

Stimuli were presented in white, against a black background. Stimulus presentation was controlled using Presentation 0.71 (Neurobehavioural Systems®) and displayed on a 15.4 inch monitor, which was placed centrally and at a distance of 50 cm from an observer.

2.5 | Design and procedure

Participants were randomly assigned to one of four groups: Anti-phase, Sham, In-phase Cz (shared return), or In-phase focal (ring return). They were blind to the kind of tAC-stimulation they received and to the existence of different groups. During the study session, each of the four participant groups underwent a short practice block and two longer experimental blocks of the task. They completed the first experimental block as a baseline (without tACS) and the second experimental block during stimulation (with one of the four tACS throughout the block). To ensure that they were comfortable with the stimulation, participants were exposed to a short period of stimulation before the start of the practice block.

2.6 | Transcranial alternating current stimulation protocols

We used a StarStim device (neuroelectrics®) where stimulation electrodes were placed at EEG-electrode positions F3 and P3 over the dorsolateral prefrontal and the posterior parietal cortex. For In-phase protocols, return electrodes over position Cz (shared return) or over positions F7, Fz, C3, P7 and Pz (ring return) were used. All eight electrodes were mounted (see Figure 2a), but depending on stimulation protocol, only a subset of electrodes was active. Round sponge electrodes with a diameter of 2.5 cm were used for stimulation. For safety reasons a 5-cm sponge electrode was used over Cz for the shared return. Impedance was kept below 10 kOhm using saline solution.

For each of the stimulation conditions there was a 30-s ramp-up phase in the beginning, until the desired intensity of stimulation was reached and a ramp-down phase over 3 s. During the active stimulation conditions, tACS was delivered constantly over the duration of the working memory task (∼14 min). The stimulation intensity is indicated as zero-to-peak. For Anti-phase stimulation over F3 and P3 (see Figure 2b, left) as previously used by Polanía et al. (2012), we delivered tACS at 6 Hz at electrode F3 with site P3 as return, such that there was a 180° phase difference between the two sites. Intensity of stimulation was 1000 μA. For Sham stimulation, within 30-s anti-phase stimulation (as described above) was ramped-up to 1000 μA, but then ramped-down within another 3 s. The stimulator did not deliver any transcranial electric stimulation after that. For In-phase Cz stimulation, the same electrode configuration as by Polanía et al. (2012) was used, that is, two stimulation electrodes were placed over electrode sites F3 and P3 with a joint return electrode over electrode site Cz. We delivered tACS at 6 Hz with 1000 μA over F3 and P3, and consequently 2000 μA at Cz. There was a 0° phase difference between F3 and P3 stimulation (see Figure 2b, middle). For the In-phase focal stimulation, we also delivered 0° phase difference tACS at 6 Hz at electrode sites F3 and P3, but four return electrodes were placed at electrode sites F7, Fz, C3, P7 and Pz. To achieve a current source density of stimulation in the dorsolateral prefrontal and the posterior parietal cortex comparable to In-phase Cz stimulation with only one shared return electrode, we delivered tACS at 1500 μA intensity over F3 and P3 and 600 μA current at each of the return electrodes stimulation (see Figure 2b, right).

Participants were blinded about their stimulation condition. Experimenters were aware of the delivered stimulation condition. To control stimulation, we used NIC2 software (neuroelectrics®) and to model the electric fields in the brain resulting from our stimulation montages, we used the integrated StimViewer software component. Thus, the electric field generated in the cortex during tACS was estimated as described by Miranda et al. (2013), using a realistic finite element model

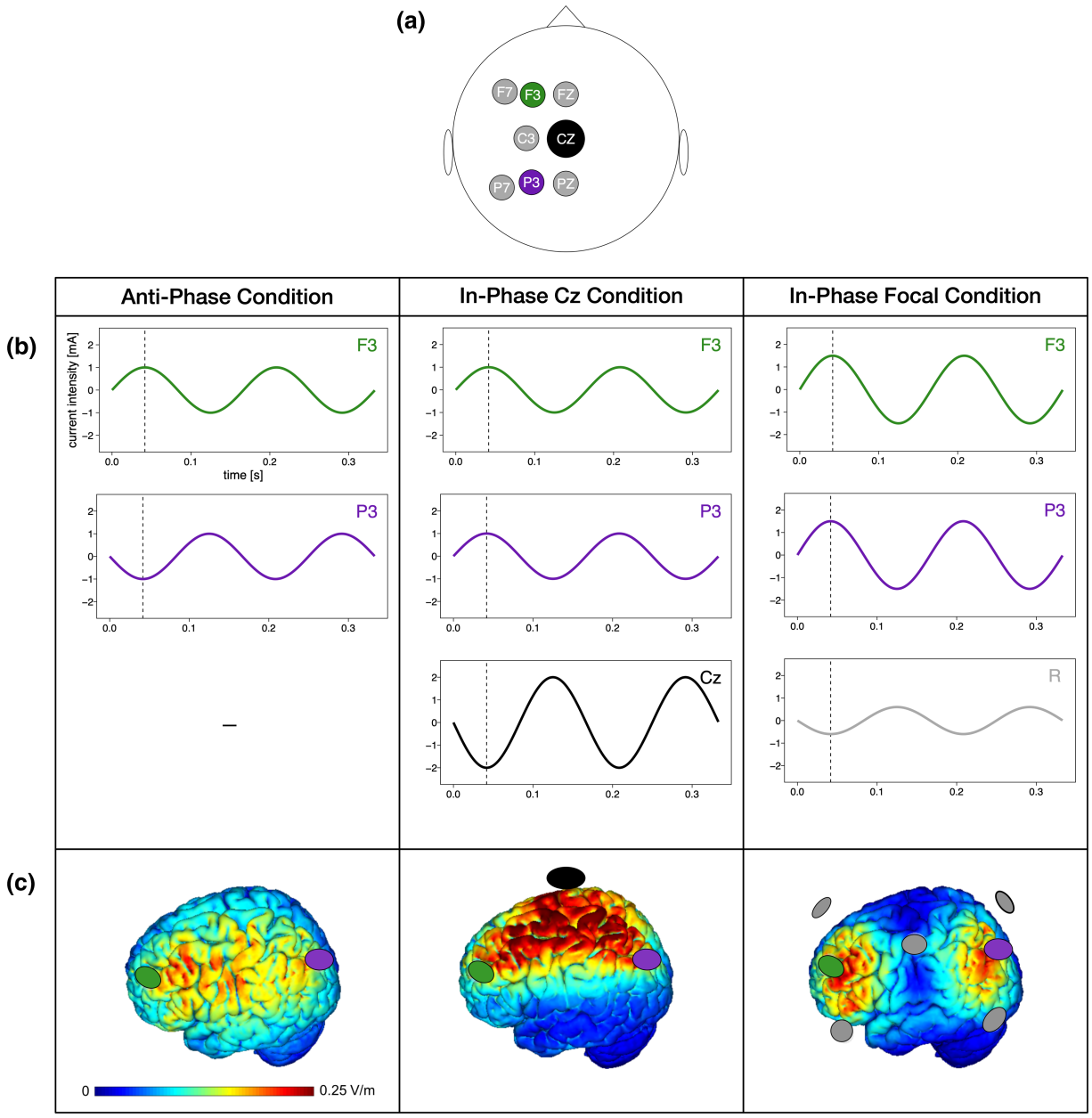

FIGURE 2 Illustration of electrode montage (a), stimulation protocols for theta (6 Hz) transcranial alternating current stimulation (tACS) (b) and electric field models (c). (a): Electrode montage. All eight electrodes were mounted, but only a subset of electrodes was used depending on stimulation protocol. Stimulation electrodes were centred over F3 (green) and P3 (violet) over the dorsolateral prefrontal and posterior parietal cortex and were used in all conditions. For the anti-phase protocol, no additional return electrode was used. For the in-phase Cz protocol, a single shared return electrode over Cz (black) was used. For the additional in-phase focal protocol, five surrounding return electrodes over F7, Fz, C3, P7 and Pz (grey) were used. Electrodes were round sponge electrodes with a diameter of 2.5 cm (but 5 cm over Cz). (b) Current intensity [mA] over time during tACS. For the anti-phase protocol, 180° phase difference theta tACS was delivered over F3 and P3 (green, violet) with an intensity of stimulation of 1000 μA. For the in-phase Cz protocol, 0° phase difference theta tACS was delivered with 1000 μA over F3 and P3, and with 2000 μA over Cz (black). For the additional in-phase focal protocol, 0° phase difference theta tACS was delivered with 1500 μA over F3 and P3 and with 600 μA over F7, Fz, C3, P7, and Pz (grey; R = return). The stimulation intensity is indicated as zero-to-peak. (c) Model of the electric field generated in the cortex during tACS, indicated as the magnitude of the electric field |E|. *Note:* Note that in the in-phase Cz condition, the stimulation intensity delivered over the shared return electrode Cz is twice as high as the stimulation intensity over F3 and P3 and that the electric field model shows the strongest effect of stimulation over central brain areas

derived from MR images (for technical details, please see Miranda et al. (2013)). Figure 2c shows the magnitude of the electric field |E| for the three active stimulation conditions.

2.7 | Data processing

To measure working memory performance, we analysed response times to probe items. Only trials with correct responses within the duration of the trial (correct button presses within 2000 ms after onset of the probe item) were included in the analysis. Overall, across participants, this led to an exclusion of 278 out of 8460 trials (3.29%; between 50 and 88 trials per stimulation condition). We checked that all response times were above 150 ms to avoid inclusion of accidental button presses, and for trials with multiple responses, the first button press was counted, which was not defined in the preregistration.

The percentage of correct responses was compared between conditions descriptively. Based on the simplicity of the task and the results reported by Polanía et al. (2012), we expected participants to perform close to ceiling.

2.8 | Statistical data analysis

Aggregated response time data were statistically evaluated using a mixed ANOVA with the within subject factor TESTPHASE (Baseline, Stimulation) and the between subject factor STIMULATION (Anti-phase, Sham, In-phase Cz, In-phase focal). In contrast to Polanía et al. (2012) who used the mean of response times across trials for their analysis, we calculated the median of response times across trials instead, as response times within subjects were not normally distributed. According to our hypotheses, we expected to find an interaction effect, driven by slower median response times during Anti-phase stimulation, but faster median response times during In-phase stimulation compared to Sham. To investigate whether the Null hypothesis or the alternative hypothesis are more likely, we computed Bayes factors (BF_{10}), quantifying how well H1 predicts the empirical data relative to H0. If BF_{10} values are above 1, they indicate evidence for H1 over H0, whereas values below 1 suggest the opposite. For BF_{10} values above 3 or below .33, the strength of evidence is regarded as noteworthy, whereas values between .33 and 3 are considered as inconclusive evidence for any hypothesis (Jeffreys, 1961; Lee & Wagenmakers, 2014). We compared the models including the interaction term against the null model that no factor, except the random factor Subject-ID, has an effect.

In addition to the pre-registered analysis on aggregated response times, we also analysed the response time distribution using Bayesian mixed effects models. An advantage of mixed effects regression models is that they allow modelling single trial data, which enabled us to make use of the whole response time distribution instead of collapsing multiple observations into a single summary score for central tendency. For this more sensitive single-trial analysis, we used Bayesian mixed effects models as they allowed us to specify an assumed ex-Gaussian distribution, which is well suited for modelling response time distributions that are right-skewed (Balota & Yap, 2011). The ex-Gaussian distribution is the convolution of the Gaussian and exponential distribution. Here, the distribution mean is modelled by parameter μ and the standard deviation of the Gaussian component is modelled by parameter σ, which correspond to the localization and variability of the distribution, respectively. The mean of the exponential component is modelled by parameter τ, which corresponds to the right tail of the distribution. Based on our hypotheses, in this distributional analysis, we investigated whether there was an interaction effect of TESTPHASE and STIMULATION condition on the μ parameter, that is, the location of the distribution. Additionally, we analysed whether such an interaction would affect the σ parameter, that is, the spread of the distribution, or the τ parameter, that is, the right tail of the distribution. We used a Bayesian mixed effects regression model where the same set of predictors were used to model each of the three parameters of the ex-Gaussian distribution. The Gaussian's location μ and spread σ, and the exponential component τ were predicted by the fixed effects TESTPHASE (baseline, stimulation), STIMULATION (Anti-phase, Sham, In-phase Cz, In-phase focal), PROBE (Match, Non-match) and their interactions, as well as by TRIAL (continuous covariate). The model included a single random-effects term for the intercept of the individual subjects and parameters σ and τ were fit on the log scale. Categorical covariates were encoded with custom contrasts (STIMULATION (Anti, Sham, In-phase Cz, In-phase Focal): Sham versus Anti (−3/4, 1/4, 1/4, 1/4), In-phase Cz and In-phase Focal versus Sham (−1/2, −1/2, 1/2, 1/2), In-phase Focal versus In-phase Cz (0, 0, −1/2, 1/2); TESTPHASE (Baseline, Stimulation): Stimulation versus Baseline (−1/2, 1/2)); PROBE (Match, Non-match): Non-match versus Match (−1/2, 1/2)), and the continuous covariate TRIAL was centred, such that the intercept is estimated as the grand average across all conditions. Thus, resulting fixed effect estimates can be interpreted as main effects. Parameter estimates for a

given effect can be interpreted as substantial if their credible intervals do not contain zero.

All analyses were carried out using statistical software R 4.04 (R Core Team, 2019). Data was visualized using the ggplot2 package 3.3.3 (Wickham, 2016). Preregistered ANOVA analyses were completed using the afex package .28.1 (Singmann et al., 2021) and Bayes Factors were computed with the BayesFactor package .9.12.4.2 (Morey & Rouder, 2018) using default priors. Bayesian mixed effects regression models were implemented with the brms package 2.14.4 (Bürkner, 2017, 2018) using default priors. We ran four chains per model, each for 2000 iterations, with a warm-up period of 1000 iterations, and initial parameter values set to 0. If necessary, we increased the number of iterations to 4000 and the treedepth to 15 until the model converged with no divergent transitions (all $\hat{R}$ values <1.01).

3 | EXPERIMENT 2: WITHIN SUBJECTS EXPERIMENT

3.1 | Aims of experiment 2

We investigated the same research questions in a second experiment. Here, we aimed to reproduce the study protocols used by Polanía et al. (2012) even more closely. Therefore, we used a within-subjects design like in the study by Polanía and colleagues where participants returned to the lab in multiple sessions. In addition to the delayed letter recognition task, we also administered a more challenging 3-back working memory task (see below). We chose this difficult n-back condition since in a previous study by Violante et al. (2017), a 'synchronization-desychronization-effect' had only been partly replicated in a 2-back task, so we chose to increase task difficulty to $n = 3$.

3.2 | A priori power analysis

While this follow-up within-subjects experiment 2 was not pre-registered, we closely followed the study protocols from the pre-registered between-subjects experiment 1. The power analysis for a repeated measures ANOVA with 4 levels (stimulation condition) suggested a minimal sample size of 20 participants, each being tested in four separate experimental sessions during the stimulation conditions. As described in experiment 1 and based on previously reported effects in the literature, we again used an estimate of effect size of $f = .2735$, a significance level of $\alpha = .05$ and a power of $1 - \beta = .80$.

3.3 | Participants

We tested 23 healthy participants in experiment 2. As in experiment 1, participants were recruited by opportunity sampling mainly within the student community of the Ludwig-Maximilians-University Munich, Germany. Inclusion criteria as described in Antal et al. (2017) were applied and the age-range for inclusion was defined as 18 to 40 years. Two participants did not continue with the study after their first session and one participant had to be excluded due to being older than the pre-defined age range. Thus, the remaining sample consisted of 20 participants (12 female, 8 male, 0 diverse) with a mean age of 24.45 years (SD = 4.74, range: 20–36 years). All of them were right handed, as assessed by the Edinburgh Handedness Inventory (Oldfield, 1971). All gave written informed consent prior to their participation and received course credits upon completion. The study was approved by the local Ethics Review Board and conducted according to the Declaration of Helsinki.

3.4 | Task and stimuli

In experiment 2a, the experimental paradigm was identical as for experiment 1, namely the same delayed letter recognition task (see Figure 1), as described above in detail. In experiment 2b, however, participants completed a 3-back task (see Figure 3). For this 3-back task, we used digits 0 to 9 as stimuli, which were sequentially presented in the centre of the screen for 500 ms, with an inter-stimulus-interval of 1,000 ms. Stimuli were presented equally often. Targets occurred in 25% of trials and were defined as those stimuli where the digit in the current trial was identical to the digit three trials earlier. Participants had to respond by button press whenever a target appeared and to refrain from pressing the button when the stimulus was not a target. Overall, the task consisted of 160 trials. A practice block of 20 trials was completed beforehand. All stimuli were presented in white, against a black background. Stimulus presentation was controlled using Presentation 0.71 (Neurobehavioural Systems®) and displayed on a 15.4 inch monitor, which was placed centrally and at a distance of 50 cm from an observer.

3.5 | Design and procedure

In four separate sessions, participants completed all four stimulation conditions (Sham, Anti-phase, In-phase Cz (shared return) or In-phase focal (ring return)).

Participants, but not experimenters, were blind to the kind of tAC-stimulation they received. The order of sessions was pseudo-randomized across participants (see Table 1). A session took place at least 2 days but on average around 6 days after the previous session (average: 5.92 days, SD = 3.82). On average, the difference for session 1 to session 2 was 6.19 days (SD = 4.63), for session 2 to session 3 it was 5.81 days (SD = 3.34), and for session 3 to session 4 it was 5.76 days (SD = 3.55). In each of the four sessions, participants completed both experiment 2a and experiment 2b. In a pseudo-randomized order, half of the participants started with experiment 2a and the other half with experiment 2b. Both experiments consisted of a short practice block and one longer experimental block. The experimental block was completed during stimulation (with one of the four tAC-stimulations throughout the block).

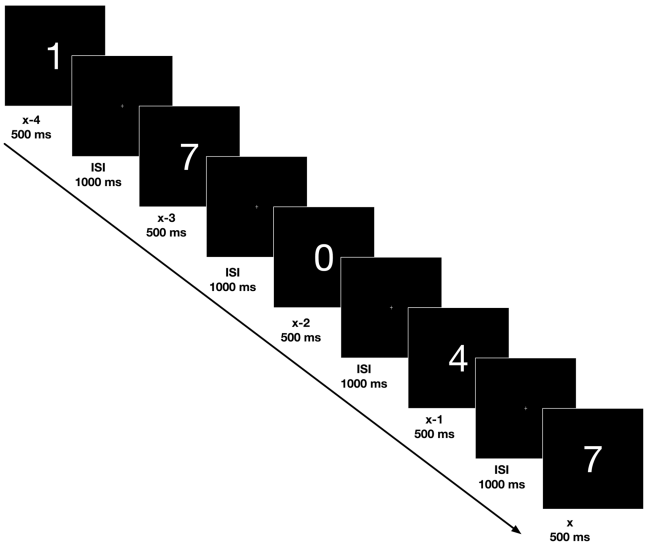

FIGURE 3 Exemplary trial sequence of the task from experiment 2b. In this 3-back task, the presented digits had to be continuously remembered and updated. The task was to indicate whether a target was presented on the current trial x, that is, when the presented digit was identical with the digit which had been presented in trial $x - 3$, so 3 trials before. This example shows a target in the current trial

3.6 | Transcranial alternating current stimulation protocols

We used the same tACS protocols as in experiment 1 (see above).

3.7 | Data processing

For experiment 2a, accuracy and response time data from the delayed letter recognition task were pre-processed and analysed as in experiment 1. The percentage of correct responses was calculated and compared between conditions descriptively. To measure working memory performance, we analysed response times following probe items. For trials with multiple responses, the first button press was counted and it was checked that all response times were above 150 ms to avoid inclusion of accidental button presses. Trials with incorrect or no responses within the duration of the trial (2 s after probe item) were excluded from analysis. Overall, across participants, this led to an exclusion of 222 out of 7560 trials (2.94%; between 52 and 65 trials per stimulation condition).

For data of experiment 2b, all trials of the 3-back task were included in the analysis. Responses (no or yes) were coded as correct or incorrect. For a descriptive analysis of task performance, we computed signal detection theory indices based on the number of hits, misses, correct rejections and false alarms. Discriminability indices were calculated as $d' = z\,(\text{Hit rate}) - z\,(\text{False alarm rate})$ and response bias indices were calculated as $c = -(z\,(\text{Hit rate}) + z\,(\text{False alarm rate}))\ /2$, where adjustments for extreme values were applied as implemented in the R package psycho (Makowski, 2018).

3.8 | Statistical data analysis

For experiment 2a, in analogy to the pre-registered analysis of experiment 1, aggregated response time data were statistically evaluated using a within-subjects ANOVA with the within subject factor STIMULATION (Anti-phase, Sham, In-phase Cz, In-phase focal). We expected

TABLE 1 Pseudo-randomized order of stimulation protocols across the four sessions

	Session order I	Session order II	Session order III	Session order IV
Session 1	In-phase Cz	Sham	Anti-phase	In-phase focal
Session 2	In-phase focal	In-phase Cz	Sham	Anti-phase
Session 3	Anti-phase	In-phase focal	In-phase Cz	Sham
Session 4	Sham	Anti-phase	In-phase focal	In-phase Cz

to find an effect of stimulation condition showing slower median response times during Anti-phase stimulation, but faster median response times during In-phase stimulation compared to Sham. To investigate whether the Null hypothesis or the alternative hypothesis are more likely, we computed the Bayes factor (BF_{10}), comparing the model including the fixed effect against the null model that no factor, except the random factor Subject-ID, has an effect.

Additionally, we again conducted a more sensitive single-trial analysis by analysing the distribution of single-trial response times from experiment 2a using Bayesian mixed effects models with an assumed ex-Gaussian distribution. We asked whether there was an effect of STIMULATION on the μ parameter, that is, the location of the distribution, but also investigated potential effects on the σ parameter, that is, the spread of the distribution, or the τ parameter, that is, the right tail of the distribution. For this, the same set of predictors were used to model each of the three parameters of the ex-Gaussian distribution. The parameters μ, σ and τ were predicted by the fixed effects STIMULATION (Anti-phase, Sham, In-phase Cz, In-phase focal), PROBE (Match, Non-match) and their interaction, as well as SESSION (continuous covariate) and TRIAL (continuous covariate). The model included a random-effects term for the intercept of the individual subjects and parameters σ and τ were fit on the log scale. Categorical covariates were encoded with custom contrasts (STIMULATION: Sham vs. Anti (−3/4, 1/4, 1/4, 1/4), In-phase Cz and In-phase Focal vs. Sham (−1/2, −1/2, 1/2, 1/2), In-phase Focal vs. In-phase Cz (0, 0, −1/2, 1/2); PROBE: Non-match vs. Match (1/2, −1/2)), and continuous covariates SESSION and TRIAL were centred. As the intercept is estimated as the grand average response times across all conditions, resulting fixed effect estimates can be interpreted as main effects.

For the statistical analysis of data from experiment 2b, for both the discriminability indices and response bias indices, assumptions for repeated-measures ANOVA were violated. Therefore, non-parametric Friedman tests were computed for discriminability and response bias, where we expected to find an effect of the within subject factor STIMULATION (Anti-phase, Sham, In-phase Cz, In-phase focal). And to investigate whether the Null hypothesis or the alternative hypothesis are more likely, we computed Bayes factors (BF_{10}), comparing the models including the fixed effect against the null models only including the random factor Subject-ID.

In an additional analysis, single-trial responses (no, yes) from experiment 2b were analysed using a Bayesian logistic mixed-effect regression that separated response bias (overall odds of responding yes) from discriminability (odds of responding yes when a target was presented). Response bias was represented by the intercept, discriminability was coded in the fixed effect TARGET (No, Yes), and we examined the interactions of bias and discriminability with STIMULATION (Anti-phase, Sham, In-phase Cz, In-phase focal), their interaction with SESSION (continuous covariate), as well as their interaction with TRIAL (continuous covariate). The model included a random-effects term for the intercept of the individual subjects. Categorical covariates were encoded with custom contrasts (TARGET: Yes vs. No (−1/2, 1/2); STIMULATION: Sham vs. Anti (−3/4, 1/4, 1/4, 1/4), In-phase Cz and In-phase Focal vs. Sham (−1/2, −1/2, 1/2, 1/2), In-phase Focal vs. In-phase Cz (0, 0, −1/2, 1/2)), and the continuous covariates SESSION and TRIAL were centred. Thus, the intercept is estimated as the grand average response bias across all conditions and resulting fixed effect estimates can be interpreted as main effects.

4 | RESULTS

4.1 | Results experiment 1 (between subjects)

Table 2 and Figure 4 show a descriptive summary of task accuracy (percentage of correct responses) and response times (median across correct trials' RTs). Task accuracy was overall high (average values in all conditions were above 95%, Table 2). For response times, we investigated whether there was an interaction effect of STIMULATION group and TESTPHASE. Results from the pre-registered ANOVA analysis indicated that overall response times were slower during the baseline than during the stimulation phase (TESTPHASE: $F[1,43] = 26.71$, $p < .001$, $\eta^2_G = .04$). No other effect was significant (STIMULATION: $F(3,43) = .62$, $p = .6$, $\eta^2_G = .04$; STIMULATION × TESTPHASE: $F(3,43) = .11$, $p = .96$, $\eta^2_G < .001$). The Bayes Factor analysis in fact indicated that there was substantial evidence that the null model was more likely to the model including the interaction STIMULATION × TESTPHASE ($BF_{10} = .12$). Similarly, there was strong evidence favouring the null model over the model including the interaction and the main effect STIMULATION ($BF_{10} = .05$), but only when including the main effect TESTPHASE along with the main effect STIMULATION the interaction term, then there was decisive evidence that the alternative hypothesis was more likely than the null hypothesis ($BF_{10} = 308.28$). And the alternative hypothesis was even more likely than the null hypothesis when including TESTPHASE as the only main effect along with the interaction term

TABLE 2 Average task accuracy and response time without stimulation (baseline) and during stimulation for all four stimulation groups in experiment 1

			Percent correct		Reaction time	
STIMULATION	**TESTPHASE**	***N***	**Mean**	**(SD)**	**Mean**	**(SD)**
Anti-phase	Baseline	11	97.07	(2.12)	548.74	(86.91)
Anti-phase	Stimulation	11	97.88	(2.19)	517.84	(83.76)
Sham	Baseline	12	96.02	(2.25)	535.26	(73.57)
Sham	Stimulation	12	97.96	(1.24)	502.10	(59.67)
In-phase Cz	Baseline	11	96.26	(2.45)	550.12	(88.53)
In-phase Cz	Stimulation	11	96.57	(2.60)	522.93	(80.97)
In-phase focal	Baseline	12	95.09	(5.67)	571.86	(83.44)
In-phase focal	Stimulation	12	96.76	(2.86)	547.40	(62.42)

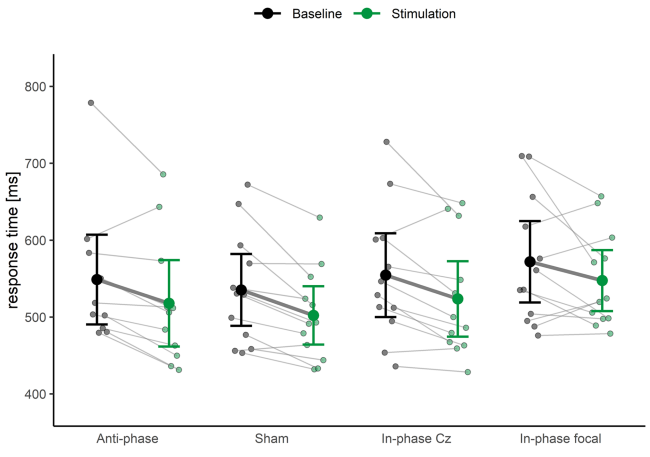

FIGURE 4 Response times (RTs) without stimulation (baseline) and during stimulation for all four stimulation groups in experiment 1. RTs were calculated as the median of RTs from correct responses. Individual subjects' scores are overlaid with the group average and 95% confidence intervals as thick lines

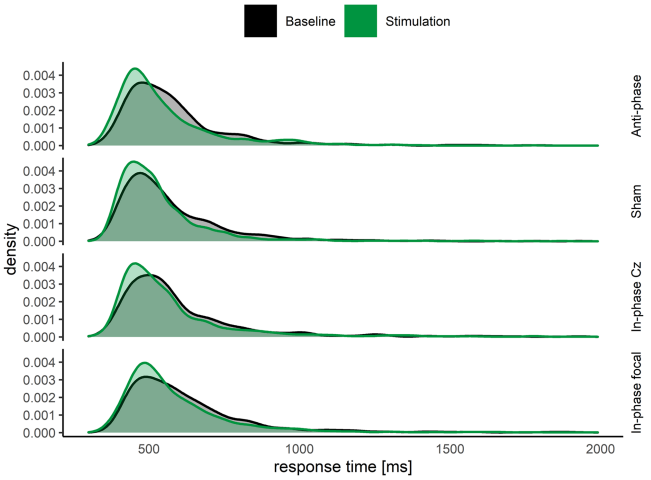

FIGURE 5 Distribution of single-trial response times (RTs) without stimulation (baseline) and during stimulation for all four stimulation groups in experiment 1

($BF_{10} = 531.4$), which indicates that mainly the large effect of TESTPHASE was influential.

In the additional ex-Gaussian regression analysis, we investigated whether there was an interaction effect of STIMULATION group and TESTPHASE on the μ parameter, that is, the location of the distribution. Additionally, we analysed whether such an interaction affected the σ parameter, that is, the spread, or the τ parameter, that is, the right tail of the distribution. The distribution of single-trial response times is shown in Figure 5. The Bayesian mixed-effects regression model converged well, yielding R-hat values around 1 and solid posterior predictions. Table S1 in the supplemental materials shows the model summary and conditional effects are visualized in Figure 6.

Results of the ex-Gaussian regression analysis indicated that for the μ parameter of the ex-Gaussian distribution there was no a substantial interaction effect involving STIMULATION group and TESTPHASE. Similar to this, neither the σ parameter nor the τ parameter showed substantial interaction effects involving STIMULATION group and TESTPHASE.

There was a substantial main effect of TESTPHASE on the μ parameter, estimating μ parameter values as faster during the stimulation phase than the previous baseline phase (Stimulation vs. Baseline: $B = -26.06$, $EE = 2.37$, $CI = [-30.65, -21.42]$). In non-match trials, μ parameter values were estimated as slower than in match trials (Non-match vs. Match: $B = 61.75$, $EE = 2.40$, $CI = [57.10, 66.68]$), and this difference was larger in the In-phase focal group than in the In-phase Cz group (In-phase Focal vs. In-phase Cz × Non-match vs. Match: $B = 14.05$, $EE = 6.93$, $CI = [.12, 27.28]$). Across stimulation groups, participants were also estimated as getting faster across trials, that is, increasing

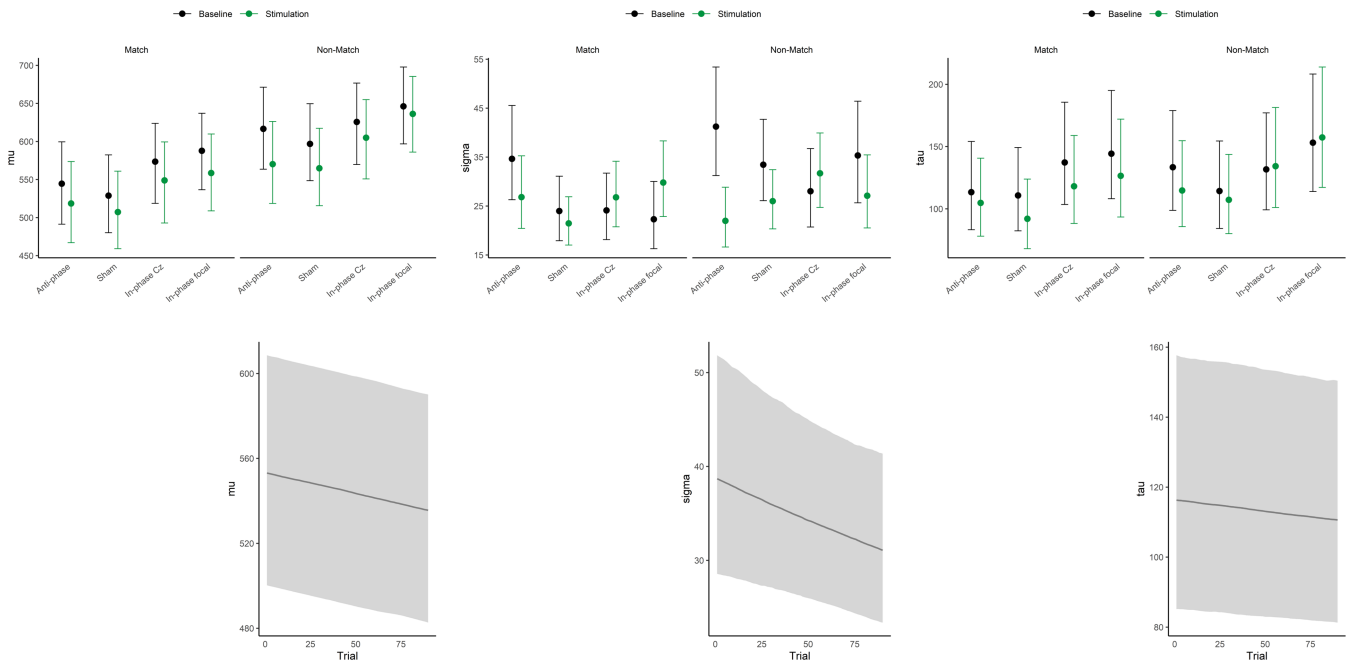

FIGURE 6 Conditional effects estimated by the ex-Gaussian regression model in experiment 1. Conditional effects are shown for all three parameters of the ex-Gaussian distribution (mu, sigma, tau). Note that none of the parameters showed an interaction effect of STIMULATION group (anti-phase, sham, in-phase Cz, in-phase focal) and TESTPHASE (baseline, stimulation) that would be in line with the a-priori hypotheses

duration of the task (trial: B = −5.18, EE = 1.09, CI = [−7.24, −3.04]). Finally, there was a 3-way interaction (In-phase Cz and In-phase Focal vs. Sham × Stimulation vs. Baseline × Non-match vs. Match: B = 22.29, EE = 10.46, CI = [2.00,42.54]), indicating that, while the μ parameter values were estimated as faster during the stimulation phase than the previous baseline phase, this difference was similar for both the In-phase stimulation groups and the Sham stimulation group during match trials; but during non-match trials, the In-phase stimulation groups showed an even smaller effect of test phase than the Sham group, contrary to what was expected (see Figure 6).

Estimates for the σ parameter of the ex-Gaussian distribution also showed a substantial main effect of TESTPHASE (Stimulation vs. Baseline: B = −.12, EE = 0.06, CI = −0.24, 0]), showing lower estimates for the stimulation phase than the previous baseline phase. This estimated difference was larger for non-match trials than for match trials (Stimulation vs. Baseline × Non-match vs. Match: B = −0.26, EE = .11, CI = [−.48, −.04]). They were also overall larger for non-match trials than match trials (Non-match vs. Match: B = .15, EE = .06, CI = [.03, .27]). Additionally, the σ parameter was estimated to decrease across trials (trial: B = −.06, E = .03, CI = [−.12, −.01]). Similarly, estimates for the τ parameter of the ex-Gaussian distribution were lower for the stimulation phase than baseline phase (Stimulation vs. Baseline: B = −.09, EE = .02, CI = [−.13, −.04]) and this estimated difference was also slightly larger for non-match trials than for match trials (Stimulation vs. Baseline × Non-match vs. Match: B = .10, EE = .04, CI = [.01, .18]). Overall τ parameters were larger for non-match trials than for match trials (Non-match vs. Match: B = .1, EE = .03, CI = [.05, .15]).

4.2 | RESULTS EXPERIMENT 2A (WITHIN SUBJECTS)

Table 3 and Figure 7 show a descriptive summary of task accuracy (percentage of correct responses) and response times (median across correct trial's response times). Overall, task accuracy was high (the average in all conditions was above 96%, Table 2). For response times, we investigated whether there was a main effect of STIMULATION condition. The repeated-measures ANOVA did not yield a significant effect (STIMULATION: F[3,60] = .87, p = .46, η^2_G = .008). The Bayes Factor analysis suggested that there was substantial evidence for the null model being more likely than the model including the effect STIMULATION (BF_{10} = .15).

In the ex-Gaussian regression analysis, we investigated whether there was an effect of stimulation

TABLE 3 Task accuracy and response times during stimulation for all four stimulation conditions in experiment 2a

		Percent correct		Reaction time	
STIMULATION	***N***	**Mean**	**(SD)**	**Mean**	**(SD)**
Anti-phase	20	97	(2.01)	511.75	(92.89)
Sham	20	97.17	(2.09)	522.20	(103.21)
In-phase Cz	20	96.44	(3.41)	530.96	(93.93)
In-phase focal	20	97.22	(2.66)	514.03	(77.82)

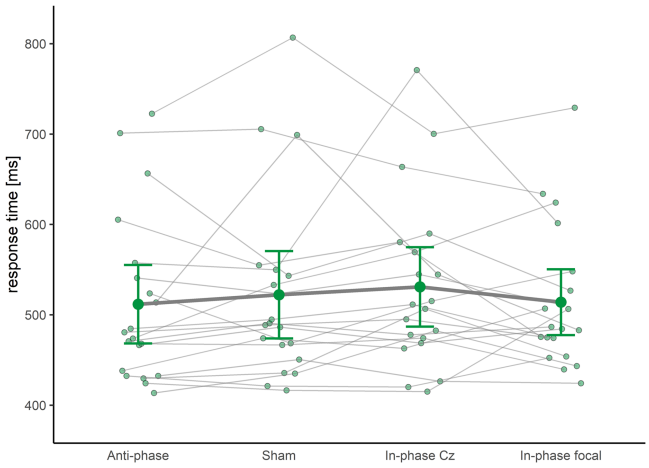

FIGURE 7 Response times (RTs) during stimulation for all four stimulation conditions in experiment 2a. RTs were calculated as the median of RTs from correct responses. Individual subjects' scores are overlaid with the group average and 95% confidence intervals as thick lines

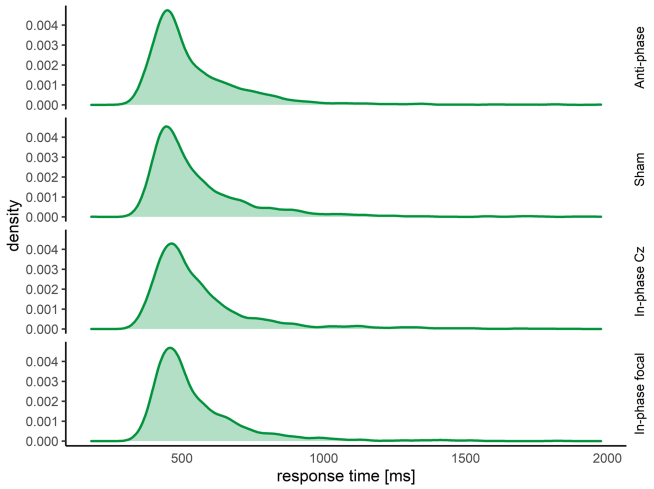

FIGURE 8 Distribution of single-trial response times (RTs) during stimulation for all four stimulation groups in experiment 2a

condition on the μ parameter, that is, the location of the distribution. Additionally, we analysed whether stimulation condition would affect the σ or the τ parameter, the spread or the right tail of the distribution, respectively. The distribution of single-trial response times is visualized in Figure 8. The Bayesian mixed-effects model converged well, yielding R-hat values around 1 and solid posterior predictions. The model summary is shown in Table S2 in the supplemental materials and conditional effects are visualized in Figure 9.

Results of the ex-Gaussian regression analysis indicated that for the μ parameter of the ex-Gaussian distribution, there was a substantial effect indicating that μ parameter values in the Sham condition were estimated as slower than in the Anti-phase condition, contrary to what was expected (Sham vs. Anti: B = 7.44, EE = 2.87, CI = [1.82, 13.13]). Additionally, the μ parameter was estimated as slower in Non-match trials than in Match trials (Non-match vs. Match: B = 55.72, EE = 2.07, CI = [51.7, 59.83]); participants were getting faster across sessions (Session: B = −12.13, EE = 1.06, CI = [−14.21, −10.02]) and slower with increasing task duration (Trial: B = 5.57, EE = 1.04, CI = [3.52, 7.6]). However, no other effects involving the factor STIMULATION were substantial for the μ parameter.

For the σ parameter of the ex-Gaussian distribution there were no substantial effects involving stimulation condition. Estimates for the σ parameter were smaller for non-match than for match trials (Non-match vs. Match: B = −.12, EE = .06, CI = [−.24, −.11]) and decreased across sessions (Session: B = −.14, EE = .03, CI = [−.2, −.08].

Estimates for the τ parameter of the ex-Gaussian distribution were overall larger for Non-match trials than for Match trials (Non-match vs. Match: B = .13, EE = .02, CI = [.09, .18]), and this difference was less pronounced in the In-phase conditions compared to the Sham condition (In-phase Cz and In-phase Focal vs. Sham × Non-match vs. Match: B = −.11, EE = .05, CI = [−.22, −.01]). And τ estimates also slightly increased across trials (Trial: B = .06, EE = .01, CI = [.04, .09]), but no other effects involving stimulation condition were substantial for the τ parameter.

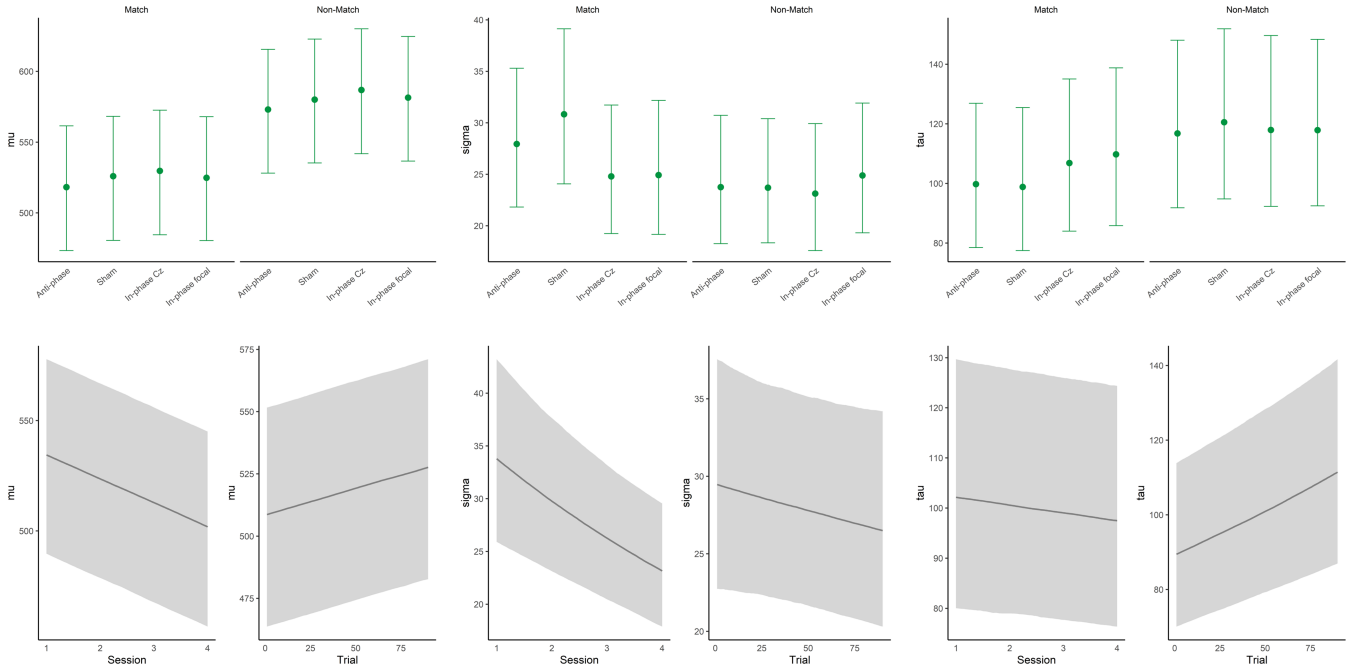

FIGURE 9 Conditional effects estimated by the ex-Gaussian regression model in experiment 2a. Conditional effects are shown for all three parameters of the ex-Gaussian distribution (mu, sigma, tau). Note that none of the parameters showed a main effect of STIMULATION condition (anti-phase, sham, in-phase Cz, in-phase focal) that would be in line with the a-priori hypotheses

4.3 | Results experiment 2b (within subjects)

A descriptive summary of discriminability (d′ index) and response bias (c index) is shown in Figure 10 and Table 4. Non-parametric Friedman tests yielded no significant effects for stimulation condition, neither for d′ (STIMULATION: χ^2 [3] = 3.76, p = .29, n = 20, Kendall's W = .06) nor for c (STIMULATION: χ^2 [3] = .929, p = .818, n = 20, Kendall's W = .02). The Bayes Factor analysis for response bias indicated strong evidence favouring the H0 over H1 (BF_{10} = .13). However, for the discriminability index, the Bayes Factor indicated that evidence remained inconclusive (BF_{10} = .47).

The more sensitive analysis of single-trial responses (no, yes) using a Bayesian logistic mixed-effect regression allowed us to separate response bias (overall odds of responding yes) from discriminability (odds of responding yes when a target was presented), and we investigated their interaction with stimulation condition. The model converged well, yielding R-hat values around 1 and solid posterior predictions. The model summary is shown in Table S3 in the supplemental materials and stimulation effects are visualized in Figure 11.

Results of the logistic regression analysis showed that nonsurprisingly, due to the low number of target trials, there was an overall response bias to respond 'no' (intercept: B = −1.2, EE = .11, CI = [−1.4,−.98]) which was estimated as slightly decreasing across trials (Trial: B = −.08, EE = .03, CI = [−.14,−.03]. Discriminability was overall high (Yes vs. No: B = 3.13, EE = .06, CI = [3.01,3.24]) and was modulated by stimulation condition such that participants responded yes when a target was presented more often while they received In-phase stimulation (focal as well as with a Cz reference) than during Sham stimulation (Yes vs. No × In-phase Cz and In-phase Focal vs. Sham: B = .37, EE = .13, CI = [.11,.64]), in line with our a-priori hypotheses. We therefore computed post-hoc interaction contrasts from the model, separately for each In-phase stimulation condition compared to Sham stimulation. These further confirmed our a-priori hypotheses: Discriminability was indeed higher while participants received In-phase focal stimulation compared to Sham stimulation, as indicated by an estimate of .45 whose 95% highest posterior density interval (HPDI) did not overlap with zero (Yes vs. No × In-phase Focal vs. Sham: B = .45, HPDI = [.13, .75]. However, the post-hoc interaction contrast comparing discriminability during the traditional In-phase Cz stimulation compared to Sham was not as conclusive. It yielded a smaller estimate of .3 whose HPDI included zero (Yes vs. No × In-phase Cz vs. Sham: B = .3, HPDI = [0, .6]).

Discriminability also improved across sessions (Yes vs. No × Session: B = .43, EE = .06, CI = [.32,.54]) and decreased across trials (Yes vs. No × Trial: B = −.22, EE = .06, CI = [−.33, −.11]).

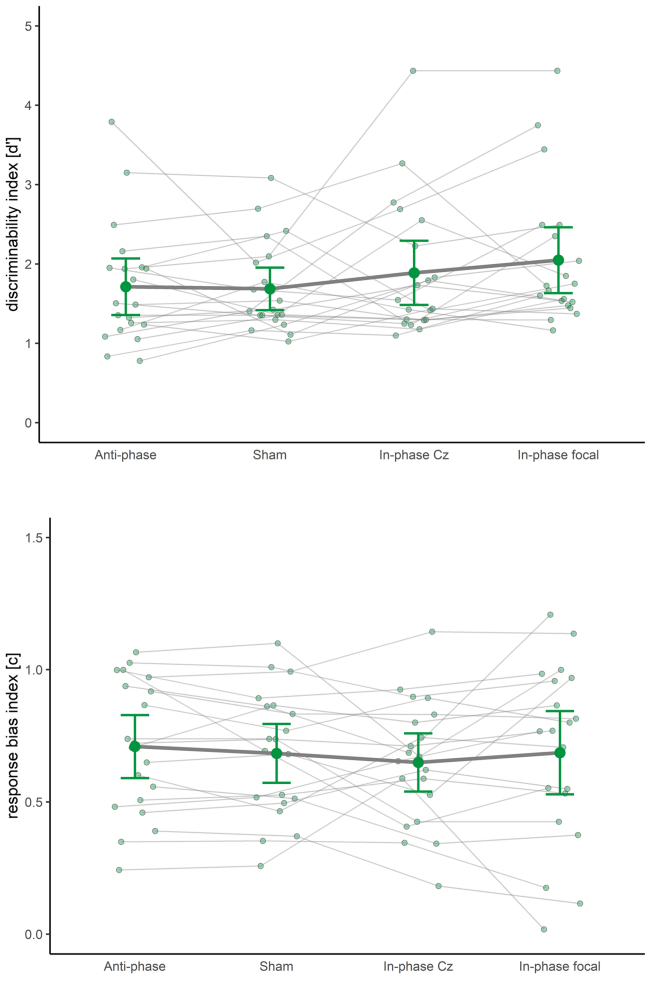

FIGURE 10 Task performance in experiment 2b, measured as discriminability d′ (upper panel) and response bias c (lower panel) during stimulation for all four stimulation conditions. Individual subjects' scores are overlaid with the group average and 95% confidence intervals as thick lines

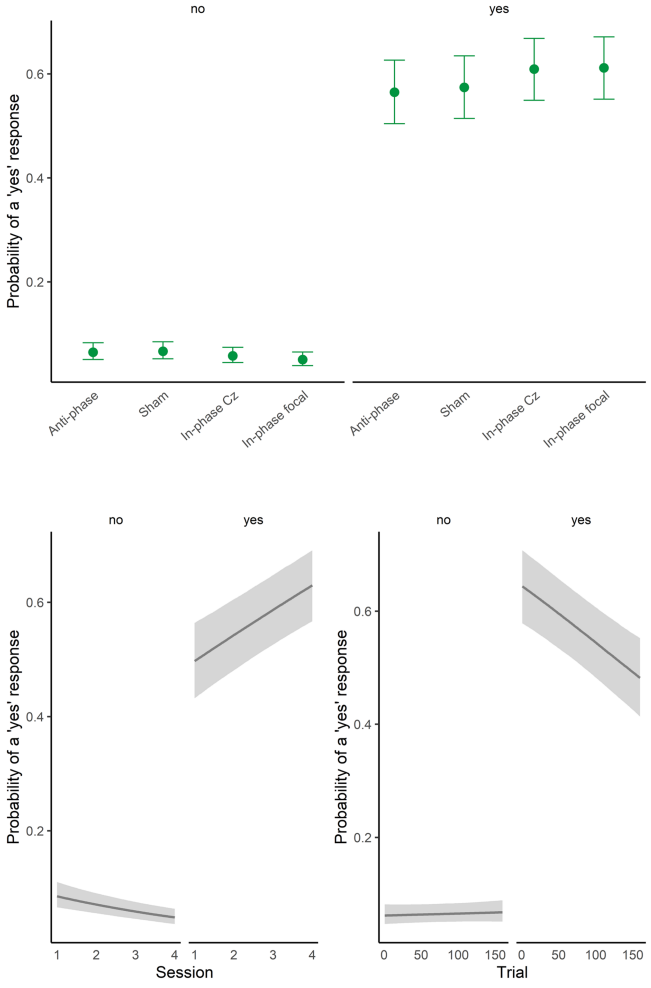

FIGURE 11 Conditional effects estimated by the model in experiment 2b. Note the interaction effect of STIMULATION condition (anti-phase, sham, in-phase Cz, in-phase focal) and TARGET (no, yes), in line with the a-priori hypotheses, showing larger discriminability for in-phase stimulation compared to sham. For all pairwise interaction contrasts, please see Table S4 in the supplemental materials

TABLE 4 Task performance in experiment 2b, measured as discriminability (d′) and response bias (c) during stimulation for all four stimulation conditions

		Discriminability		Response bias	
STIMULATION	*N*	Mean	(SD)	Mean	(SD)
Anti-phase	20	1.71	(.76)	.71	(.25)
Sham	20	1.69	(.57)	.68	(.24)
In-phase Cz	20	1.89	(.86)	.65	(.24)
In-phase focal	20	2.05	(.88)	.69	(.34)

5 | DISCUSSION

In this study, we applied transcranial alternating current stimulation (tACS) at theta frequency for exogenously modulating oscillatory activity in a fronto-parietal network that is engaged in working memory performance. We aimed to reproduce the findings reported by Polanía et al. (2012) and to investigate whether a more focal in-phase stimulation, as suggested by electric field modelling (Saturnino et al., 2017), will have at least as much of a facilitatory effect as the in-phase stimulation utilized by Polanía and colleagues. Highlighting the importance of theta oscillations for working memory performance, Polanía et al. (2012) showed that in a left-hemispheric fronto-parietal theta-network, in-phase theta tACS led to shorter response times whereas anti-phase stimulation led to longer response times compared to a placebo stimulation. Against our hypothesis, we found no decrease of response times by an exogenous boost of left-hemispheric

fronto-parietal theta coupling nor an increase of response times by an exogenous induction of a 180° relative phase, using the same delayed letter discrimination task and stimulation parameters in two experiments, both between-subjects and within-subjects. Surprisingly, instead of impairment through asynchronous theta tACS, response times in the within-subjects experiment were even slightly faster in the anti-phase stimulation condition than in the sham condition, which is the opposite from what was expected regarding the hypothesized 'synchronization-desynchronization' effect. However, in the same experiment, task performance in a demanding 3-back task (the odds of correctly detecting a target) was substantially improved for in-phase theta tACS compared to the sham condition, which is in line with our a-priori hypothesis, whereas we observed no decrease of performance through anti-phase theta tACS.

Similarly, 'synchronization-desynchronization' effects on response times using fronto-parietal theta tACS have not been or only partly been reproduced in previous studies (Alekseichuk et al., 2017; Kleinert et al., 2017; Violante et al., 2017). Kleinert et al. (2017) reported that their data from a visuospatial delayed match-to-sample task showed no significant differences in response times between the stimulation conditions. Violante et al. (2017) found an effect of tACS condition on response times in the more demanding 2-back task, but not so in the less demanding 1-back task. However, there was only an improvement in the in-phase stimulation group, but no impairment during anti-phase tACS. Similar to this, we observed an improvement of task performance (the odds of correctly detecting a target) for in-phase tACS in the 3-back task in experiment 2b, but no impairment of performance during anti-phase tACS. In contrast to this, Alekseichuk et al. (2017) found that anti-phase theta tACS led to increased response times and reduced accuracy in a 2-back task, whereas in-phase tACS had no beneficial effect.

This could mean that a 'synchronization-desynchronization' effect on response times might be smaller in effect size than previously expected, requiring larger sample sizes than in the current and the aforementioned studies to be detected. However, in this study, a Bayes Factor analysis showed conclusive evidence that the null-hypothesis predicted the empirical data better than the research hypothesis, given the current sample size in the between-subjects experiment ($n = 46$) and the within-subjects experiment ($n = 20$). Additionally, we even conducted a single-trial regression analysis in which we investigated whether there was an effect of stimulation on the location of the response time distribution and also on two additional parameters comprising the variability and the right tail of the distribution. Yet, we did not observe a substantial 'synchronization-desynchronization' effect on either parameter of the response time distribution, nor a trend in that direction. And inconsistent findings have also been reported in the literature using other types of frequency-tuned in-phase or anti-phase stimulation. While it was reported that in-phase alpha-band stimulation over the right frontal and parietal cortex compared to sham stimulation modulated response times and fronto-parietal coherence during a spatial attention task (van Schouwenburg et al., 2017), these effects could not be reproduced in a second study, nor was there a modulation by anti-phase alpha tACS condition (van Schouwenburg et al., 2018).

A common criticism about studies using a single return electrode for two stimulation electrodes is that the phase lag between the two active sites is not the only parameter that varies between in-phase stimulation (using a single return electrode for two stimulation electrodes) and anti-phase stimulation (where the two active stimulation electrodes function as a return for themselves). For example, it has been criticized that between in-phase and anti-phase conditions there could be variations in the direction of current flow (Thut et al., 2017), and it has been pointed out that differences in the overall intensity of stimulation could not be ruled out (Kleinert et al., 2017), potentially leading to the observed differences between conditions. These criticisms have been demonstrated to be very valid using in vivo recordings in the macaque brain (Alekseichuk et al., 2019). And following from electric field modelling (Saturnino et al., 2017), it has been pointed out that for in-phase tACS with a single return electrode for two stimulation electrodes, as used in this study and by previous researchers (Polania et al., 2012; Kleinert et al., 2017; Violante et al., 2017), it might not be the fronto-parietal network that is primarily stimulated.

Therefore, the central goal of our study was to investigate whether fronto-parietal focal in-phase tACS, for which we positioned multiple close-by return electrodes to focally stimulate the frontal and the parietal cortex, would result in a facilitation of working memory performance. Previously, van Schouwenburg et al. (2017) had used three lateral central reference electrodes (C2, C4, C6) located in-between the stimulation electrodes (F4, P4) and others had proposed the use of centre-surround ring montages (Bortoletto et al., 2016; Saturnino et al., 2017). We surrounded the stimulation electrodes (F3 and P3) with five return electrodes close-by (F7, Fz, C3, P7, Pz). By modelling the electric field in the brain associated with our stimulation protocols, we confirmed that this montage was capable of producing a focal electric field targeting frontal and parietal cortices. However, for response times in the delayed letter discrimination

task, our data neither showed a facilitatory effect of in-phase stimulation (shared return and focal) compared to a sham condition, nor a difference between focal in-phase tACS and in-phase tACS with a shared return electrode or a trend or descriptive difference pointing in that direction.

Since this focal in-phase theta tACS with multiple close-by return electrodes produced no modulation of response times compared to sham stimulation and no benefit over in-phase stimulation with a shared return, it is possible that it might be less effective than suggested by Saturnino et al. (2017). One suggestion for future research could be to utilize fully closed ring montages (Bortoletto et al., 2016; Saturnino et al., 2017) instead. However, although we saw no modulatory effect on response times in the letter recognition task whatsoever, we did indeed observe a slight improvement of discriminability in the 3-back task during the in-phase theta tACS conditions compared to the sham condition in the single-trial regression analysis. And interestingly, this was more strongly driven by the fronto-parietal focal in-phase tACS with multiple close-by return electrodes: Pairwise interaction contrasts indicated a substantial improvement of discriminability during in-phase focal theta tACS compared to sham stimulation, but a less conclusive and overall smaller improvement of discriminability during the In-phase Cz condition compared to sham. Although there was no substantial difference between the focal in-phase stimulation and the in-phase stimulation with a shared return electrode when compared directly because the difference was small, we take this as evidence supporting our second hypothesis, that relative to sham stimulation focal fronto-parietal theta tACS lead to at least as much of an improvement in task performance as the traditional montage, if not more.

So given that we were able to show some facilitatory effect in the more demanding 3-back task, what could be a more plausible and rather general limitation of this study is that the task adapted from Polanía et al. (2012) was a very easy task. This is corroborated by accuracy rates above 95% for the delayed letter recognition task in both experiments, which is close to ceiling. For the 3-back task, however, average discriminability (d′) values were between 1.7 and 2, which is not close to ceiling performance, indicating that an improvement of performance would, in general, be possible. This may explain why we find a facilitatory effect of in-phase tACS, but no further detrimental effect. Interestingly, effects of task difficulty or participant characteristics have been previously reported in the literature. For example, previously discussed reports also pointed into the direction that an improvement of reaction times by in-phase theta stimulation was only found in a more demanding 2-back task, but not in the less demanding 1-back task (Violante et al., 2017). Similarly, for gamma tACS, an improvement for a more demanding 3-back task following stimulation has been found, but not in a less demanding 2-back condition (Hoy et al., 2015), or for more complex trials involving logical reasoning (Santarnecchi et al., 2013, 2016). For fronto-temporal theta tACS which had been delivered in-phase, an improvement in working memory accuracy was observed for older adults and only for those younger adults who were low-performing, whereas detrimental effects of anti-phase stimulation could be shown for high-performing younger adults (Reinhart et al., 2019). Similarly, it has also been reported that improved performance in a visual–spatial memory task during in-phase theta tACS between left and right parietal cortex was observed for low-performers, whereas high-performers showed decreased WM performance during anti-phase theta tACS between left and right parietal cortex (Tseng et al., 2018). And such differences between high and low performers regarding their sensitivity for enhancing or detrimental effects due to in-phase or anti-phase tACS were observed for gamma tACS (Tseng et al., 2016). Along with the findings from our study, this evidence underlines that task difficulty and individual performance levels of a given sample might determine whether facilitatory effects through in-phase tACS and detrimental effects of anti-phase tACS will be observed. For future studies, it might be therefore well advised to individually adjust task difficulty to the performance level of each participant. Another parameter for future investigations would be to include an additional anti-phase stimulation protocol which also uses a ring of return electrodes. Such an electrode montage should achieve an even more focal stimulation of the frontal and parietal cortex and should potentially increase the chance to observe detrimental effects of asynchronous stimulation.

While other studies used experimental paradigms and targeted other cortical sites than in the seminal study by Polanía et al. (2012), the approach we used in the current study was very similar to the one by Polanía et al. (2012). One small difference was that repeated sessions within participants occurred with a least 5 days difference (Polanía et al., 2012) compared to at least 2 days difference in the current study. However, it is not clear how this would result in an absence of any stimulation effect on response times. Rather, this might contribute to the observed improvement of task performance across sessions (see below for a discussion). One critical difference, however, could be that in the in-phase stimulation condition, we used a slightly larger sponge electrode as a shared return electrode for two stimulation electrodes. We chose this larger electrode to reduce the current

density under the reference electrode. Saturnino et al. (2017) demonstrated that using one shared return electrode for two stimulation electrodes might lead to the strongest stimulation effect under the return electrode and not under the active electrodes placed over fronto-parietal regions. Our in-phase montage aimed to reduce this effect. One could speculate that the increase of working memory performance observed by Polanía et al. (2012) might have been partly driven by a boost of fronto-central theta activity in the in-phase condition, induced through the stronger current density under the central reference electrode location. Particularly frontal-midline theta activity, which has been shown to be essential in working memory processes (Berger et al., 2019), could have been entrained by this kind of stimulation. Another mechanism could potentially be that in the stronger current density under the central reference electrode location with reversed polarity might have enabled a de-coupling of default-mode network hubs over central areas with the fronto-parietal working memory network. The default mode network has been associated with slow frequency coherence in the delta to alpha range (Das et al., 2020; Kim et al., 2014; Samogin et al., 2019), and more specifically, areas of the default-mode and fronto-parietal network have been shown to be related to theta band connectivity (Kam et al., 2019). This might also explain the absence of a modulation of response times during in-phase tACS in our study, where we used the larger return electrode. A rather general limitation of our and previous studies is that sham-blinding during transcranial electrical stimulation protocols may be less effective than previously expected (Greinacher et al., 2019; Turner et al., 2021). Instead of the traditional fade-in, short stimulation, fade-out sham protocol where possible, future studies should aim to adopt 'active controls'.

In addition to the discussed effects (and nil effects) for stimulation group or stimulation condition, we observed a couple of substantial effects involving covariates. In experiment 1, we observed an effect of test phase, such that average response times, the spread and the right tail of the distribution decreased from the baseline phase to the subsequent phase where stimulation was delivered, reflecting practice effects. Similarly, average response times and their variability in experiment 2a decreased across sessions and discriminability in experiment 2b increased across sessions, indicating that upon repetition of the task, participants improved in performance. However, the training duration in the current study was not much shorter than in a previous study using the same task (Polanía et al., 2012). Still, it could be beneficial to extend the training phase, especially because it has been reported that practice effects across sessions can outweigh effects of tACS or tDCS (Röhner et al., 2018). For the effect of trial, results were a bit more variable. Whereas participants from experiment 1 improved across trials, showing increasingly faster and less variable response times, performance in experiment 2 decremented across trials, with increasingly slower response times in experiment 2a and decreasing discriminability in experiment 2b across trials. This might result from different effects of fatigue between the recruited samples of participants, since study participation was overall more demanding for participants in experiment 2, who returned to the lab four times and completed two task paradigms each session, including the more demanding 3-back task. In both experiments, response times for trials in which the probe did not match the cued memory item were longer, and more skewed; whereas concerning the spread of the response time distributions, they were slightly more variable in experiment 1 or slightly less variable in experiment 2a. But since responses were given by the right index finger for match trials or the right middle finger for non-match trials, this could be simply due to differences in responsiveness of index and middle fingers.

This trivial effect was also involved in several interactions. In experiment 1, for both the variability and the right skewness of the distribution, the difference between stimulation phase and the previous baseline phase was larger for non-match trials than for match trials, which is plausible considering that the middle finger might be less responsive than the index finger. For average response times, the difference between non-match and match trials was larger in the In-phase focal group than in the In-phase Cz group, but this did not interact with test phase. And while average response times were faster during the stimulation phase than during the previous baseline phase, during match trials this difference was similar for both the In-phase stimulation groups and the Sham stimulation group, but during non-match trials, the In-phase stimulation groups showed an even smaller effect of test phase than the Sham group, contrary to what could be expected. Conversely, in experiment 2, only for the right skewness of the distribution, the difference between non-match and match trials was less pronounced in the In-phase conditions compared to the Sham condition. It is possible that all these interaction effects between the non-match versus match trials and the stimulation condition contrasts could be driven by differences in electric field strength and spread across motor areas between the different stimulation montages.

Interestingly, while we could not reproduce a 'synchronization-desynchronization' effect by fronto-parietal theta tACS on response times in a delayed letter recognition task, we could show that in a more demanding 3-back task, in-phase and in-phase focal theta tACS

improved discriminability substantially compared to a sham condition. A 'synchronization-desynchronization' effect through in-phase or anti-phase tACS was reproduced, at least partly, both for working memory by fronto-parietal theta tACS (Alekseichuk et al., 2017; Röhner et al., 2018; Tseng et al., 2018; Violante et al., 2017) but also for other cognitive domains; such as for semantic retrieval performance by fronto-parietal theta tACS (Marko et al., 2019), for executive functions by frontal theta tACS (Reinhart, 2017), for spatial attention by fronto-parietal alpha tACS (van Schouwenburg et al., 2017), or for motion perception through parieto-occipital gamma and alpha tACS (Helfrich et al., 2014; Salamanca-Giron et al., 2020; Strüber et al., 2014). Especially those studies reporting an improvement in working memory performance for older adults and low-performing individuals (Reinhart & Nguyen, 2019; Tseng et al., 2016, 2018) are quite promising for future therapeutic applications. However, it is challenging that results have been relatively inconsistent so far. And, intriguingly, behavioural modulation due to anti-phase stimulation has sometimes been characterized by an enhancement effect on performance instead of showing detrimental effects (Salamanca-Giron et al., 2020; Tseng et al., 2016; Yaple & Vakhrushev, 2018). Depending on the actual phase lag between two stimulated brain areas, either in-phase or anti-phase stimulation might be most beneficial. But most likely, a precise tuning of exact phase lag and the precise frequency at which stimulation gets delivered should result in the strongest effects. Thereby phase lag as well as frequency might demonstrate considerable inter-individual differences which would be important to account for in future brain stimulation studies.

Overall, we did not directly reproduce findings originally reported by Polanía et al. (2012) in this study. Nevertheless, the study by Polanía and colleagues is without doubt a milestone article which has had a tremendous influence on non-invasive brain stimulation. It was one of the first studies that tried modulating more complex distributed network activity, beyond mere entrainment of local amplitude of oscillatory activity. This has opened up an entirely new avenue of research aiming on modulating yet more complex oscillatory brain activation patterns, such as cross-frequency coupling (Alekseichuk et al., 2016; de Lara et al., 2018; Turi et al., 2020). Moreover, here we demonstrated that the basic mechanism described in Polanía et al.'s (2012) seminal paper can be found when cognitive task demands are high enough. This indicates that phase-sensitive electric brain stimulation can potentially be used for increasing peak performance or for compensating cognitive decline.

ACKNOWLEDGEMENTS

This work was funded by Deutsche Forschungsgemeinschaft (DFG) SA 1872/2-2. We thank the LMU Students (Anna Behringer, Leonie Bonn, Raffaela Böswald, Anita Flack, Katja Frey, Charlotte Fromm, Marlene Försterling, Judith Gans, Robin Knauf, Chiara Linke, Svea Meyer, Kirsten Moser, Anna Noack, Anna Redkina, Alina Schwedas, Pamela Stoyanova) for their support with data collection.

CONFLICT OF INTEREST

The authors declare no competing interests.

AUTHORS' CONTIBUTIONS

Anna Lena Biel: Conceptualization, Methodology, Software, Validation, Investigation, Data Curation, Formal analysis, Writing–Original Draft, Visualization, Project administration; Elisabeth Sterner: Investigation, Data Curation, Writing–Review & Editing; Lukas Röll: Investigation, Writing–Review & Editing; Paul Sauseng: Conceptualization, Methodology, Software, Validation, Investigation, Resources, Writing–Review & Editing, Supervision, Funding acquisition.

PEER REVIEW

The peer review history for this article is available at https://publons.com/publon/10.1111/ejn.15563.

DATA AVAILABILITY STATEMENT

The data and analysis scripts that support the findings of this study are openly available in our project repository on Open Science Framework (https://osf.io/4z7wk/).

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How to cite this article: Biel, A. L., Sterner, E., Röll, L., & Sauseng, P. (2022). Modulating verbal working memory with fronto-parietal transcranial electric stimulation at theta frequency: Does it work? *European Journal of Neuroscience*, *55*(2), 405–425. https://doi.org/10.1111/ejn.15563