Effects of parietal exogenous oscillatory field potentials on subjectively perceived memory confidence

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1. Introduction

Scientific studies have established the importance of theta (3–7 Hz) oscillations in investigating the neural basis of memory. Power and phase locking of theta signals are important for encoding of information and are positively correlated to memory accuracy, source memory, retrieval speed and subjectively perceived confidence (Caplan & Glaholt, 2007; Lin et al., 2017; Osipova et al., 2006; Rutishauser, Ross, Mamalak, & Schuman, 2010; Scholz, Schneider, & Rose, 2017; Staudigl & Hanslmayr, 2013; Sweeney-Reed et al., 2016; Wynn, Daselaar, Kessels, & Schutter, 2019). Furthermore, the presence of theta oscillations during the retrieval of information is associated with more detailed recollection of information, as well as higher rates of subjective perceived confidence (Addante, Watrous, Yonelinas, Ekstrom, & Ranganath, 2011; Gruber, Tsivilis, Giabbiconi, & Muller, 2008; Guderian & Duzel, 2005; Herweg et al., 2016; Osipova et al., 2006; Wynn et al., 2019). In addition to the positive relation between theta oscillations and memory performance accuracy, the aforementioned studies have also demonstrated the close connection between theta activity and experienced confidence in recognition. In a previous study we recorded theta oscillations while healthy volunteers performed a recognition task and were instructed to provide confidence rating regarding ‘old/new’ decisions. Results showed that theta power over the posterior parietal regions during retrieval was positively correlated to subjectively perceived memory confidence (Wynn et al., 2019). These findings replicate and extend prior work on the direct link between the parietal cortex and metmemory (Chua, Schacter, & Sperling, 2009; Chua, Schacter, Rand-Giovannetti, & Sperling, 2006; Rutishauser, Aflalo, Rosario, Pournatian, & Andersen, 2018). In one of these studies, single-cell recordings in the posterior parietal cortex of tetraplegic patients during picture recognition showed that parietal neurons are sensitive to self-reported confidence levels (Rutishauser et al., 2018).

To examine the functional contribution of theta oscillations to memory processes more directly, transcranial alternating current stimulation (tACS) can be used through administering weak exogenous sinusoidal oscillatory fields (Herrmann, Rach, Neuling, & Struber, 2013; Schutter, 2014). Empirical studies have, for example, shown that parietal alpha (9.5–11.3 Hz) tACS can phase-lock neural activity and locally increase alpha power (Helfrich et al., 2014; Zaehele, Rach, & Herrmann, 2010). Even though theta tACS has not yet been used in the context of recognition memory, it has been shown to alter performance in working memory tasks (Hanslmayr, Axmacher, & Inman, 2019). For instance, theta tACS has been successfully applied to improve working memory capacity in healthy volunteers (Jausovec & Jausovec, 2014; Jausovec, Jausovec, & Pahor, 2014). Moreover, Wolinski, Cooper, Sauseng, and Romei (2018) showed in a sham-controlled study that
4 Hz tACS over the parietal cortex enhances, while 7 Hz parietal tACS reduces visuospatial working memory capacity. The latter findings suggest that functions targeted by parietal tACS are closely linked to the intrinsic frequency of the underlying neural processes.

Additional exploratory analysis of our previously published data set (Wynn et al., 2019) indicated that on average the highest accuracy and subjectively perceived confidence ratings were associated with 3.5 Hz activity over the posterior regions during retrieval. Thus, if 3.5 Hz over the posterior parietal cortex is indeed critically involved in subjectively perceived confidence in recognition memory, then tACS applied at this frequency should alter the subjective recognition experience. To address this issue, we performed a double-blind sham-controlled within-subjects study in healthy volunteers, to test the hypothesis that 3.5 Hz tACS will enhance subjectively perceived confidence. Given the link between theta oscillations and various memory-related processes, our secondary research goal was to test whether 3.5 Hz tACS improves item or source memory. This secondary research goal enables us to explore to what extent tACS affected objective memory-related processes. In addition, we explored after-effects of 3.5 Hz tACS on resting state EEG to examine potential activity changes in the theta frequency range.

2. Methods

2.1. Participants

Fifty-four healthy adult right-handed volunteers (38 women) with a mean age of 21.3 (SD = 2.7) completed this study. All had normal or corrected-to-normal vision, were native Dutch speakers, non-smokers and free from self-reported neurological or psychiatric conditions. Main exclusion criteria were skin disease, metal in cranium, epilepsy or a family history of epilepsy, history of other neurological conditions or psychiatric disease, heart disease, use of psychoactive medication or substances; pregnancy. All participants were recruited through the website of the Radboud Research Participation System. The exclusion criteria were mentioned on this website and again in contact prior to participation, therefore all of the volunteers who came to the lab were pre-screened on the exclusion criteria. One participant dropped out after the first session for undisclosed reasons. Data from this participant was excluded and replaced with data from a new participant, leaving 54 participants in the final analyses.

Stimulation parameters were in agreement with the International Federation of Clinical Neurophysiology safety guidelines (Rossi, Hallett,
Rossini, Pascual-Leone, & Safety of, 2009). The study was approved by the medical ethical committee of the Radboud University Medical Center, Nijmegen, the Netherlands, and carried out in accordance with the standards set by the Declaration of Helsinki.

2.2. Memory task

Stimuli were presented on a personal computer screen with a 21-in. monitor. Stimulus presentation and recording of responses were attained using PsychoPy (v1.80; Peirce et al., 2019). The stimulus material consisted of 400 words per session, varying per participant, randomly chosen from a pool of 1444 words, selected from the MRC Psycholinguistic Database (http://websites.psychology.uwa.edu.au/school/MRCDatabase/uwa_mrc.htm) and translated into Dutch. All words in this database are scored on word frequency, familiarity, and concreteness, which combined leads to an ‘imageability’ rating between 100 and 700 (Coltheart, 1981). We only included nouns that had a rating of > 500. Three parallel versions of unique lists of words for encoding and retrieval were randomly generated separately for each participant.

The recognition task was designed to evaluate the effects of tACS on multiple memory measures. Our primary objective concerned subjectively perceived memory confidence, therefore participants indicated their confidence levels on a visual-analogue scale. This increases sensitivity of the confidence measurement in comparison to Likert scales. In addition, considering the association between theta oscillations and source memory (Addante et al., 2011; Gruber, Tsivilis, Giabbiconi, & Müller, 2008), possible tACS effects on source memory were investigated. To this end, encoding items were presented on various screen locations, and the memory of which was tested afterwards.

2.3. TACS parameters

TACS was delivered by a battery-driven constant DC current stimulator (Eldith DC Stimulator (CE 0118), Ilmenau) using three electrodes (2 × 25 cm², 1 × 100 cm²) in saline-soaked synthetic sponges at an 3.5 or 8 Hz alternating current intensity of 2 mA (peak-to-peak) for 30 min. TACS was administered via two active electrodes over P7 and P8 electrode sites and one reference electrode centred over Cz. The maximal duration of the stimulation was 30 min including a ramp up and ramp down period of 15 s, in which the intensity was gradually increased to 2 mA peak-to-peak. During sham tACS, the 15-second ramp up period was followed by 30 s of real stimulation, after which the intensity was ramped down in 15 s to 0 mA. Impedance was kept under 10 kΩ throughout the experiment (impedance at the start of stimulation: M = 7.21, SD = 3.22).

In the retrieval phase, participants performed a recognition task, including the 200 ‘old’ words that were presented during encoding and 200 ‘new’ words (see Fig. 2). The retrieval trials started with the presentation of a fixation cross of which the duration was randomly selected from an uniform distribution (M = 1000 ms, range = 900–1100 ms, increment = 50 ms), and thereafter the one second presentation of a word. The words were presented at random positions in the 4 × 4 grid on the screen, and the cue informed the participants about the upcoming location of the word. Each participant performed 200 encoding trials, while making a semantic classification (‘natural’ or ‘artefact’) regarding the presented word (see Fig. 2). The semantic classification of the stimuli ensured that participants kept attending to the presented stimuli. Participants used the left and right mouse button, of which the response binding was randomized and counterbalanced over participants.

During the retrieval phase, target (3.5 Hz), sham and control (8 Hz) tACS were administered via two active electrodes over P7 and P8 electrode sites and one reference electrode centred over Cz. The maximal duration of the stimulation was 30 min including a ramp up and ramp down period of 15 s, in which the intensity was gradually increased to 2 mA peak-to-peak. During sham tACS, the 15-second ramp up period was followed by 30 s of real stimulation, after which the intensity was ramped down in 15 s to 0 mA. Impedance was kept under 10 kΩ through the experiment (impedance at the start of stimulation: M = 7.21, SD = 3.22).

In the retrieval phase, participants performed a recognition task, including the 200 ‘old’ words that were presented during encoding and 200 ‘new’ words (see Fig. 2). The retrieval trials started with the presentation of a fixation cross of which the duration was randomly selected from an uniform distribution (M = 500 ms, range = 400–600 ms, increment = 50 ms). This was followed by a centrally presented word and a visual analogue scale. Participants were instructed to use this scale to indicate whether they thought the word was ‘old’ or ‘new’, taking into account the confidence they had in their decision. The far left indicated ‘very sure old’ and the far right indicated ‘very sure new’. Participants could adjust their answer until pressing the ‘accept’ button, or until five seconds had passed since the onset of the word. When their final response was on the right ‘new’ side of scale, the next trial started after their decision was finalized. When their final response was to the left ‘old’ side of the scale, the 4 × 4 grid reappeared on the screen with the current word presented at a random position. Participants then had 5 s to drag the word to the position they thought it had appeared during encoding. They could finalize their decision by a mouse click on the indicated position.

To familiarize participants with the task, twenty practice trials preceded both the encoding and retrieval phase of the experiment. Stimuli used during the practice trials were not used in the
experimental trials. Following every 100 experimental trials there was a short break of at least 30 s, resulting in approximately 10 min of encoding and 30 min of retrieval. The interval between the encoding and retrieval phase was approximately seven minutes. At the end of the third session volunteers were debriefed and received compensation for participation.

2.6. Data reduction and analyses

Data analyses were performed with the use of MATLAB (v2015b, MathWorks Inc., Natwick MA) in combination with the FieldTrip toolbox (Oostenveld, Fries, Maris, & Schoffelen, 2011). Responses on the visual analogue scale were logged in values ranging from 0 to 100. Values that were smaller than 50 were classified as ‘new’ responses and values greater than 50 were classified as ‘old’ responses. On the original scale, a value of 0 represented the highest level of confidence for ‘old’ responses and a value of 100 represented the highest level of confidence for ‘new’ responses. For confidence analyses, we made the confidence ratings more directly interpretable, by rescaling the confidence ratings for both old and new items on a scale from 0 to 1. Confidence scores were calculated separately for old and new responses to represent confidence as a percentage of the maximal range of 50 (0–50 for old items and 50–100 for new items).

old: \( \frac{(50 - \text{observed response})}{50} \)

new: \( \frac{(\text{observed response} - 50)}{50} \)

Since the original scale with a range of 0–100 was reduced to two scales with a range of 0–50 and 50–100, the final ‘old’ and ‘new’ confidence ratings with a range of 0–1 had increments of 0.02.

General memory performance was quantified as d-prime score:

\[ d' = Z(\text{hit rate}) - Z(\text{false alarm rate}) \]

Performance regarding the source memory of the word position was quantified as the Manhattan distance between the actual encoding word position and the position indicated by the participant during retrieval.

Raw EEG signals were re-referenced off-line to the average of the mastoid electrodes and band-pass filtered between 0.1 and 30 Hz (roll off: 60 dB/oct). The four minutes of resting state EEG data were cut into two-second epochs. Epochs with transient muscle or electrode artefacts were rejected based on visual inspection. Ocular artefacts were removed using the default independent component analysis (ICA) in the Fieldtrip toolbox. This performs ICA on the data with the use of the logistic infomax ICA algorithm of Bell and Sejnowski (1995) supplemented by the natural gradient feature of Amari, Cichocki, and Yang (1996). With the use of ICA, components that contained ocular artefacts were identified by inspecting the time course and spatial topography of all components. After ICA components that contained ocular artefacts were removed, remaining muscle and non-neurogenic artefacts were rejected by a second visual inspection of the data. Since the focus of our stimulation was on the parietal cortex, P3, Pz, and P4 electrode sites were examined in further analyses. Spectral power was extracted using Fourier analysis with a Hanning taper. Frequencies that were assessed ranged from 2 to 30 Hz in 0.5 Hz steps. Conform the tACS frequencies, further analyses focused on the mean power at 3.5 Hz and 8 Hz.

General linear models (GLMs) for repeated measures were used to test for significant differences in item memory, confidence, source memory, and oscillatory power, between the tACS conditions. First, an RM GLM was conducted to examine the effect of stimulation (sham, control, target) on d-prime and source error. Second, in order to account for the accuracy and memory response related to the confidence score, a GLM with accuracy (correct, incorrect), memory response (old, new) and stimulation (sham, control, target) was performed. Third, To examine the effects of tACS on resting state EEG power corresponding to the tACS stimulation frequencies, a GLM analyses with time (pre-encoding, post-encoding, post-retrieval), frequency (3.5 Hz, 8 Hz) and stimulation (sham, control, target) was performed.

In case the sphericity assumption was violated, Greenhouse-Geisser corrected p-values are reported. Effect sizes (ηp²) were computed for all analyses. Only the main effect of stimulation and the interactions with stimulation were of relevance for our hypotheses, and thus only these results were analysed. When the GLM was significant, post-hoc tests were performed using Fisher’s least significant difference procedure. Alpha level of significance was set at 0.05 (two-tailed).

3. Results

The tACS procedure was well tolerated and no adverse effects occurred. Reported side effects were tingling sensations (n = 8), itching sensations (n = 1), mild dizziness (n = 1), or mild headache (n = 3). None of the participants reported visual sensations during stimulation.
Experiencing mild side effects was no exclusion criteria, therefore data of all participants was included in the final analyses. Participants were not able to reliably differentiate between real and sham tACS ($X^2(4) = 6.88, p = .14$), and additionally were not able to reliably indicate the target condition ($X^2(4) = 1.15, p = .89$).

3.1. Memory accuracy

No main effect of tACS was observed on $d$-prime ($F(2,106) = 0.16, p = .85, \eta_p^2 = 0.003, \xi = 0.87$) and source error ($F(2,106) = 0.01, p = 0.99, \eta_p^2 < 0.001, \xi = 0.81$, see Fig. 3).

3.2. Subjectively perceived confidence

A significant main effect of tACS was observed ($F(2,106) = 4.07, p = .020, \eta_p^2 = 0.071, \xi = 0.95$, see Fig. 3). Post-hoc tests showed a significant difference between memory confidence during 3.5 Hz tACS and sham tACS ($t(53) = 2.26, p = .028$), indicating that exogenous 3.5 Hz oscillations over parietal regions reduced memory confidence. In contrast, memory confidence during 8 Hz tACS did not differ from memory confidence during sham tACS ($t(53) = -1.00, p = .32$) and 3.5 Hz tACS ($t(53) = 1.24, p = .22$). None of the interactions between stimulation and the other within-subject factors reached significance (all $p$-values > 0.23). This indicates that the tACS effect on subjectively perceived memory confidence was not influenced by memory decision or accuracy (see also Table 1).

3.3. Resting state EEG

No significant tACS effects were observed for the resting state EEGs (all $p$-values > 0.18), indicating that tACS did not affect offline endogenous 3.5 Hz and 8 Hz power after stimulation (see Tables 2 and 3).

4. Discussion

In this study we set out to examine the effects of parietal 3.5 Hz tACS on subjectively perceived memory recognition. In contrast to our expectations, we showed that 3.5 Hz tACS over the parietal cortex reduced subjective recognition confidence. While the behavioural effect was opposite to our hypothesis, the frequency-specific effect of tACS concurs with the previously reported relation between parietal theta activity and memory confidence (Wynn et al., 2019). Furthermore, lesion patients who showed intact memory accuracy, but impaired memory confidence, illustrate the involvement of the parietal cortex in the subjectively experience of memory (Simons, Peers, Mazuz, Berryhill, & Olson, 2009). This is replicated in a more recent study in which the parietal cortex of healthy volunteers was perturbed with transcranial magnetic stimulation (TMS) during memory retrieval (Wynn, Hendriks, Daselaar, Kessels, & Schutter, 2018). In addition, in a recent EEG study we demonstrated the involvement of parietal theta oscillations in subjectively perceived memory confidence (Wynn et al., 2019). More specifically, this study reported a positive association between parietal theta power during memory retrieval and high-confident memory responses.

Since baseline measures and experimental variations can influence the direction of the effects of non-invasive brain stimulation (Benwell, Learmonth, Miniusi, Harvey, & Thut, 2015; Brem, Fried, Horvath, Robertson, & Pascual-Leone, 2014; Hsu, Juan, & Tseng, 2016), the paradoxical behavioural tACS effect we report might be due to state-dependent factors. One of these factors might be the phase-relationship between TACS and ongoing neural activity. In our study, tACS was not time-locked to stimulus onset, therefore the oscillatory phase at the start of stimulus processing was inconsistent. Previous studies have shown that performance gains accompany a phase-reset of endogenous oscillations in response to retrieval cues (Klimesch et al., 2004). In addition, successful encoding and retrieval processes occur at distinct phases of a theta oscillation (Hasselmo, Bodélon, & Wyble, 2002; Rizzuto, Madsen, Bromfield, Schulze-Bonhage, & Kahana, 2006). The time-invariant 3.5 Hz tACS may thus have prevented the occurrence of a precise stimulus-locked endogenous theta oscillation during retrieval. This perturbation might have led to a reduction in memory confidence. In contrast, previous work suggests that applying theta tACS in a
stimulus-locked and phase-dependent manner may in fact improve memory performance (Helfrich et al., 2014). In sum, an evoked-centred stimulation approach may more closely match the actual underlying physiology during retrieval. Alternatively, the unexpected tACS-related interference might be due to methodological factors. The target frequency was chosen based upon re-analysing data from a previous study conducted in our lab (Wynn et al., 2019) which showed the highest positive correlation with recognition confidence around 3.5 Hz. However, the task used in the current study contained fewer trials, a continuous response scale and tested source memory. In addition, the average d-prime in the current study (M = 2.04) was notably higher than in the previous study (M = 1.29). There have been instances where the effects of non-invasive brain stimulation were dependent on task difficulty (Ehls, Haueussinger, Gastel, Fallgatter, & Plewnia, 2016; Gill, Shah-Basak, & Hamilton, 2015). Therefore, it is possible that differences in recognition task performance contributed to the unanticipated interference tACS-related effect.

Functional imaging studies have reported greater parietal activation during confidence than recognition judgements (Chua et al., 2006) and during high-confident than low-confident responses (Yonelinas, Otten, Shaw, & Rugg, 2005). These findings support the hypothesis that parietal activity is related to post-retieval memory monitoring (Chua et al., 2009). Our results show an effect of parietal 3.5 Hz tACS on recognition confidence, but not on item and source memory. We propose that parietal 3.5 Hz tACS interferes with the monitoring of internally generated products of retrieval, used to guide memory decisions. When the difference between the available evidence favouring the correct and incorrect decision is small, the confidence in the decision will decrease. As long as the evidence in favour of the correct decision exceeds that of the incorrect decision, accuracy will remain high (Busey, Tunnicliff, Loftus, & Loftus, 2000; Clark, 1997).

Furthermore, the interference induced by 3.5 Hz tACS might not have been substantial enough to reduce objective recognition accuracy, due to the parietal target region. Where parietal regions are often linked to subjective memory, frontal regions have been linked to objective memory. In a previous study, functional neuroimaging was utilized to explore brain activation during confidence and recognition judgements in a memory task. This study linked parietal activation to subjective confidence judgements, while activation in the anterior cingulate and fusiform regions were related to objective recognition judgements (Chua et al., 2006). In addition, several electrophysiological studies have reported associations between frontotemporal theta power and objective memory (Addante et al., 2011; Caplan & Glaholt, 2007; Gruber et al., 2008; Guderian & Duzel, 2005). Furthermore, transcranial direct current stimulation (tDCS) over frontal regions has been shown to alter objective, but not subjective memory encoding (Gaynor & Chua, 2017). Therefore, future studies applying non-invasive brain stimulation over frontal regions have a higher likelihood of finding effects on objective memory measures.

Additionally, no observable changes in the resting state EEG power in the stimulated frequency were found after tACS. The precise mechanisms underlying the relation between the applied frequency and the endogenous rhythms after tACS remain a topic of investigation (Stecher & Herrmann, 2018; Tesche & Houck, 2017). One possibility is that other frequencies than the frequency of stimulation were a factor that other studies have reported. That other frequencies than the frequency of tACS interfered with the monitoring of internally generated products of retrieval, used to guide memory decisions. When the difference between the available evidence favouring the correct and incorrect decision is small, the confidence in the decision will decrease. As long as the evidence in favour of the correct decision exceeds that of the incorrect decision, accuracy will remain high (Busey, Tunnicliff, Loftus, & Loftus, 2000; Clark, 1997).

In conclusion, our study provides direct evidence that 3.5 Hz oscillations in the parietal cortex are involved in subjectively perceived word recognition confidence in healthy volunteers.

References


