Interleaved EEG-tACS to measure effects on theta oscillations and long-term memory

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Abstract

In post-traumatic stress disorder (PTSD), re-experiencing symptoms (i.e., reliving any aspect of the traumatic incident) play an important role. Memory consolidation of new memories into long-term memory makes the memory less liable to disruption by other stimuli and thus enhances recall. Neural oscillations between prefrontal areas, at theta-band frequencies (4-7.5 Hz), are suggested to underpin memory consolidation. Earlier studies provide evidence for cognitive improvement through modulation of brain activity with transcranial alternating current stimulation (tACS), even at different memory stages. However, its potential regarding facilitation of memory consolidation remains unclear. We aimed to investigate whether tACS at theta frequency during memory consolidation increases recall performance on a memory task with an interference component. Additionally, changes in theta-band electroencephalography (EEG) oscillatory power during resting-state was measured. In a counter-balanced crossover design, 27 healthy volunteers underwent an EEG-tACS interleaved protocol in which a total of 20-minute bi-frontal active and sham tACS (5 Hz, 2mA peak-to-peak) was administered in two separate sessions. TACS was administered during the consolidation stage of a free-recall task including emotional stimuli. Results show no significant difference between active tACS vs. sham tACS conditions on memory recall performance or EEG theta power. Our study thereby provides no evidence for enhanced memory consolidation or theta power after bi-frontal tACS administration at the theta frequency. Future studies are needed to find more optimal different tACS parameters, such as stimulation at a personalised theta frequency or a fronto-partietal electrode montage might allow for optimal conditions to modulate memory consolidation.

Keywords: memory interference; theta; transcranial alternating current stimulation

Layman's Summary

In posttraumatische stressstoornis (PTSS) zijn herbelevingssymptomen, het opnieuw beleven van traumatische gebeurtenissen in de vorm van beelden, geluiden of nachtmerries, prominent aanwezig (Creamer et al., 2011). Consolidatie, het opslaan van nieuwe herinneringen in het langetermijngeheugen, maakt de informatie minder vatbaar voor interferentie door andere prikkels zoals herbelevingen (Dudai, 2004). Vervolgens zorgt optimale geheugenconsolidatie voor verbeterde oproepbaarheid van de nieuwe informatie. Neurale oscillaties tussen prefrontale gebieden op theta-bandfrequenties (4-7,5 Hz) worden verondersteld de basis te vormen voor geheugenconsolidatie (Rozengurt et al., 2017). Eerdere studies tonen bewijs voor cognitieve verbetering door modulatie van hersenactiviteit met transcraniële wisselstroomstimulatie (tACS) in verschillende geheugenstadia (Paßmann et al., 2023; Rozengurt et al., 2017; Sahu & Tseng, 2021). TACS levert sinusvormige stimulatie aan de hoofdhuid en synchroniseert hersenoscillaties, waardoor neurale activiteit worden aangepast naar de frequentie waarmee gestimuleerd wordt (Antal & Paulus, 2013; Maiella et al., 2022). De potentiële rol van tACS in het verbeteren van geheugenconsolidatie blijft echter onduidelijk. In het huidige onderzoek, onderzochten we of tACS op theta frequentie tijdens geheugenconsolidatie het herinneringsvermogen verhoogt bij een geheugentaak met een interferentiecomponent. Daarnaast werd verandering in theta-band elektro-encefalografie (EEG) power gemeten in rust (i.e., zonder presentatie van stimuli). Zeventwintig gezonde vrijwilligers ondergingen een afwisselend EEG-tACS protocol waarin een totaal van 20 minuten bi-frontale actieve en schijn-tACS (5 Hz, 2 mA peak-to-peak) werd toegediend in twee afzonderlijke sessies. TACS werd toegediend tijdens de consolidatiefase van een vrije herinneringstaak met emotionele stimuli. Ten aanzien van tACS, verwachtte we een verhoging van de hersenactiviteit in het theta ritme en verbeterde prestaties op het herroepen van de aangeboden informatie. Resultaten tonen geen significant verschil tussen actieve en

schijn-tACS op geheugenprestaties of EEG theta power. Ons onderzoek levert dus geen bewijs voor verbeterde geheugenconsolidatie of verhoogde activiteit in het theta ritme na toediening van bi-frontale theta tACS. Toekomstig onderzoek is nodig om optimale tACS parameters te ontdekken, zoals stimulatie op een gepersonaliseerde theta frequentie of een fronto-pariëtale elektrodemontage, die het moduleren van geheugenconsolidatie mogelijk maken.

1. Introduction

Military deployment is a time of heightened risk for exposure to traumatic events (van der Wal et al., 2019) and subsequent posttraumatic stress disorder (PTSD; Creamer et al., 2011). PTSD is a disorder triggered by an extreme stressor and is characterised by a combination of intrusion, avoidance, and arousal symptoms. Prominent among these symptoms are the recurrence of traumatic experiences through intrusive thoughts or images, nightmares, dissociative flashbacks, and intense distress when confronted with reminders of the trauma (Creamer et al., 2011). The impact of PTSD on everyday mental operations is particularly devastating as it is associated with impairment in a host of critical cognitive functions including memory (Steinberg, 2005; for a review see: Hayes et al, 2012), and executive functioning (Koechlin et al., 2003; Schweizer et al., 2017). Everyday challenges tend to emerge when cognitive resources are overwhelmed by addressing these emotion driven thoughts, feelings, and behavioural urges. Although these urges are not directly relevant for the current task, they are associated with the person's problems (Mason et al., 2007). As current first-choice psychological treatment interventions for PTSD show mixed efficacy (Watts et al., 2013), specifically in those with repetitive trauma exposure such as military personnel (Haagen et al., 2015), there is a need to determine whether there are alternative means of modulating this cognitive dysfunction.

A fundamental cognitive resource involved in managing competing demands is working memory. In the context of PTSD, re-experiencing symptoms mainly manifest as visual recollections. Moreover, these intrusions are associated with visual memory and a poor ability to exercise cognitive control, for which adaptive working memory function is crucial (Mathew et al., 2022; Swick et al., 2017). For example, Honzel et al. (2014) reported less accurate scores on a dual-task in PTSD patients, relative to controls, suggesting interference of extraneous stimuli with visual memory due to limited executive control resources.

Considering the involuntary and disruptive nature of intrusive memories, a crucial inquiry pertains to whether PTSD is linked with altered control of memory interference. Altered cognitive control can lead to the inability to inhibit previously relevant information from interfering with the present context and thus preventing one to perform the current task. Memory consolidation is the stabilisation of a new acquired memory into long-term memory and subsequently makes the memory less liable to such disruption (Dudai, 2004; Robertson, 2012; Runyan et al., 2019). In accordance, enhanced consolidation processes are implicated in the persistence of and the ability to recall memories (Rozengurt et al., 2017).

Regarding clinical research in PTSD, a topic of growing interest is the use of non-invasive brain stimulation techniques (NIBS) such as transcranial electrical stimulation (tES). One significant advantage of tES is its feasibility, as well as its safety (Smits et al., 2021). By exploring the potential of tES in PTSD research, it might be possible to identify new treatment options. In the realm of tES techniques, transcranial alternating current stimulation (tACS) has emerged as a promising option for modulating endogenous oscillatory brain activity (Tavakoli & Yun, 2017; Wischnewski et al., 2023). TACS delivers sinusoidal stimulation to the scalp and entrains ongoing brain oscillations, altering neural excitability and activity, within a specific frequency (Antal & Paulus, 2013; Maiella et al., 2022). Moreover, this type of NIBS protocol could increase endogenous oscillation amplitude by applying stimulation at a frequency matching naturally occurring oscillations.

Functional neuroimaging literature shows that neural processing within a common set of brain regions, the prefrontal and parietal cortices, underly maintenance of relevant information (Alekseichuk et al., 2020; Bunge et al., 2001; Nee et al., 2007) and ignoring distracting irrelevant information (Harding et al., 2015; Menon et al., 2022). Deterioration of these functions has also been linked to lesions within this fronto-parietal network (Wager & Smith, 2003). Hence, targeting these areas might aid mitigation of PTSD intrusive symptomology. Empirical evidence indicates that the synchronisation of neural oscillatory networks induced by tACS contribute to modulation of memory performance, such as on working memory and associative memory tasks (e.g., Alekseichuk et al., 2016; Jaušovec & Pahor, 2017; Pahor & Jaušovec, 2018; Polanía et al., 2012; Sahu & Tseng, 2021; for reviews see Klink et al., 2020; Lee et al. 2023; Al Qasem et al., 2022; Senkowski et al. 2022).

Theta band activity, primarily originating in limbic structures such as the hippocampus and cingulate cortex, with generators also being found in the prefrontal cortex, reflects enhanced cognitive control demands (Cohen et al., 2011; Kerrén et al., 2022; Nigbur et al., 2011; van Driel et al., 2015). Notably, increased theta oscillations in the anterior cingulate cortex and sustained coupling with the lateral prefrontal cortex during interference tasks (i.e., when cognitive control is required to inhibit task-irrelevant information), reveal the involvement of higher-order control mechanisms in resolving response conflicts (Hanslmayr et al., 2008; Messel et al., 2021). Rozengurt and colleagues (2017) used theta neurofeedback to improve recall performance over progressively prolonged periods. During the episodic memory task subjects were visually presented with their real-time theta band power and asked to maintain this brain activity for subsequent trials when recall was successful. Results showed increased overall recall and were proposed to be supported by enhanced memory consolidation between trials, providing further evidence for theta associated memory effects. In a preliminary study by Paßmann et al. (2023) the fronto-parietal network was stimulated bi-hemispherical, in attempt to regulate the bidirectional interaction of the prefrontal cortex-hippocampus axis, and found it to induce theta band-specific benefit in memory performance for encoding. Overall, the collective evidence proposes increased theta power is consistent in various control-intensive situations, linking a network of brain areas associated with memory through oscillations with this frequency range. This underscores the potential utilisation of theta tACS in memory enhancement within those suffering from PTSD-related intrusions.

However, optimal stimulation parameters are task-dependent. For instance, tACS administered within the theta frequency-band (4-7.5 Hz) seems beneficial for working memory task performance (Alekseichuk et al., 2016; Guo et al., 2021), whereas stimulation at alpha (8-12 Hz) and beta frequency (13-30 Hz) facilitates motor sequence learning (Krause et al., 2016; Pollok et al., 2015). However, studies tend to use different stimulation parameters: frequency (4 Hz, 5 Hz, 6 Hz, or individual determined theta frequencies), intensity (1 mA, 1.5 mA, or individual determined thresholds for skin sensation due to tACS), stimulation phase (in- vs. anti-phase), and electrode configuration (left or right frontal, parietal, and fronto-parietal), while focusing on the same cognitive function. Additionally, altered theta activity is commonly measured with an electroencephalogram (EEG) during or prior to and after the task-stimulation procedure (Helfrich et al., 2014), creating variability in interpreting tACS effects. Moreover, Schutter and colleagues (2023) suggested that not only tACS parameter settings guide efficacy, but that individual differences in affective state prior to stimulation also explain a portion of the inconsistencies in results. The diversity in methodology makes it challenging to draw definite conclusions regarding tACS efficacy on memory processes.

To measure the effect of tACS on theta activity associated with memory consolidation, we recorded EEG. In the current study an interleaved EEG-tACS protocol is introduced because EEG recording while applying tACS introduces an electrical artifact at stimulation frequency in EEG signals (Fehér & Morishima, 2016) and attempts at correcting the tACS artifact cannot ensure complete removal (Vosskuhl et al., 2020). To examine whether tACS affects memory recall performance after inhibition of irrelevant stimuli, we used an emotional Free-Recall Task. We hypothesise that theta tACS upregulates theta power and thus increases performance on the memory task.

2. Method

2.1. Participants

Healthy volunteers with normal or corrected-to-normal vision were recruited for this study. Campus students were recruited via advertisements on the Social and Behavioural Sciences research participant system of Utrecht University and social media. General exclusion criteria: alcohol or substance abuse, psychoactive medication use, history or family history of epileptic seizures, other neurological disorders, colour-blindness, and dyslexia. Individuals with current psychiatric diagnosis or trauma-related disorders, were also excluded from study participation. Additionally, individuals were excluded from study participation if they met one of the following contraindications to tACS: large metal parts in the head, implanted pacemaker or neurostimulator, and pregnancy. To preclude potential confounding effects, participants were instructed to refrain from caffeine and alcohol intake or the use of nicotine substances within three hours prior to each experimental session. In attempt to raise task motivation, volunteers could win an additional 15 euros voucher in case their average performance on both tasks was best out of 10 consecutive participants.

The a priori computed sample size was 32 [computed in G*Power 3.1 (Faul et al., 2007) with $\alpha = 0.05$, $\beta = 95\%$, and Cohen's $f = 0.34$ based on prior reported results (Hsu et al., 2017, 2019; Ratcliffe et al., 2022) lowered by 10%].

Informed written consent was obtained from all participants prior to the experiment. The Faculty Ethical Commission Social Sciences of Utrecht University approved the study.

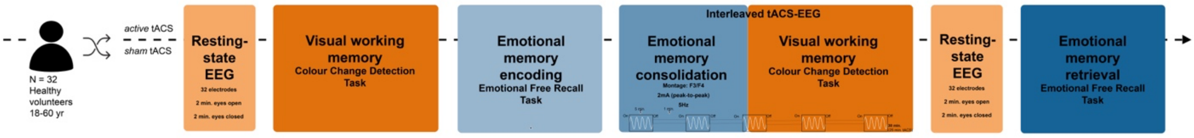
2.2. Procedure

The current study comprises a counter-balanced crossover design in which the sequence of tACS conditions (active/sham) is randomised. After screening, eligible subjects are randomly assigned to a group based on order of stimulation: active-sham tACS or sham-active tACS.

Both the investigator and the participants were blinded to the stimulation condition. Blinding was achieved through the utilisation of a five-digit code that was entered into the NeuroConn stimulator. These codes were associated with either sham or active stimulation and the randomisation code list was controlled by an independent individual within our research group. To prevent potential carry-over effects of stimulations between sessions a wash-out period of six days was implemented (Röhner et al., 2018; Živanović et al., 2022). Each participant received two appointments for two consecutive weeks. Both experimental sessions lasted approximately 90 minutes. Participants were granted a voucher (30 euros) or study credits upon completion of the second session.

After reading a short introduction participants accepted an informed consent form before starting with the baseline questionnaire (i.e., state anxiety, pre-test task motivation and mental fatigue inventories). The emotional memory task (an Emotional Free-Recall Task as described in section 2.2.1) comprised a memory encoding stage and a memory retrieval stage. At the start of the experiment, participants performed the encoding stage. Then active or sham tACS was applied. Finally, participants performed the retrieval stage. During the first half of the stimulation period, participants were instructed to look towards the screen in front of them. This phase of the experiment was denoted the consolidation stage of emotional memory as participants were now able to processes the acquired words. During the second half of the stimulation period, participants performed a visual memory task. Furthermore, 4 minutes of resting state EEG data (2 minutes eyes-open, 2 minutes eyes-closed) was recorded prior to a baseline visual memory task and stimulation, and immediately after the stimulation procedure (Figure 1A). These measurements are part of a broader research project and not analysed for the present study (for complete preregistration on Open Science Framework see https://osf.io/j459e). After the second resting-state EEG recording, the retrieval stage took place. Lastly, participants answered questions on tACS sensations and adverse effects, and after the second session also on blinding success.

A



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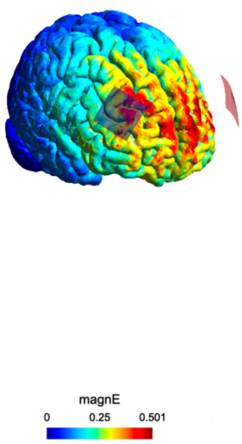


Figure 1. Study design and stimulation configuration. (A) Schematic overview of the study procedure, excluding questionnaires. (B) SimNIBS electrical field distribution simulation of tACS montage over position F3 and F4.

2.2.1. Emotional Free-Recall Task

In both experimental sessions, memory is assessed based on the performance on a novel computerised emotional Free-Recall Task (eFRT) adapted from the complex reading span tasks used in prior studies (Schweizer et al., 2019; Schweizer & Dalgleish, 2011, 2016). Similar to most complex span tasks (Conway et al., 2005), the eFRT includes a memory component expecting participants to memorise and recall information. However, in our experimental paradigm information is to be stored and retrieved over a prolonged retention interval and thereby taxing long term memory mechanisms. Simultaneously, the operation component of the task requires participants to perform a relatively simple cognitive task that may interfere with the capacity to memorise the to-be-remembered information. Generally, this to-be-remembered material consists of single words, whereas the operation task involves processing complete sentences.

Encoding stage.

In the eFRT participants were asked to memorise a set of words that were later tested by free recall. To create an emotional interference context, memorisation words were presented in conjunction with a neutral or emotionally negative sentence which participants had to evaluate on semantic correctness. Trials were spread over two conditions: neutral sentences and emotional sentences adapted from the Dutch translations of the Self-Compassion Scale–Short Form (SCS-SF; Raes et al., 2011), the Self-Esteem Rating Scale-Short Form (SERS-SF; Lecomte et al., 2006), and the Rosenberg Self-Esteem Scale (RSE; Franck et al., 2008). The emotional sentences were related to evaluation or liking of oneself in (negative) affective terms (Rosenberg, 1965) (e.g., “I certainly feel useless at times.”), and the neutral sentences comprising neutral facts (e.g., “The sun rises in the east.”). These sentences were either semantically correct or incorrect. Incorrect sentences were altered by replacing a word with a semantically incorrect word in the sentence context (e.g., “Anderen doen *stoel* beter dan ik.” [I feel that others do *chair* better than I do.] or “Boeketten bevatten veel *tafels*.” [Bouquets contain a lot of *tables*.]; italic font for illustration purposes only). Care was taken that these substitutions in the sentences were made in different positions, to avoid prediction of where to look for anomalies. Notably, in all cases the basic meaning of a sentence remained apparent.

Per trial, participants were instructed to first evaluate the sentence (semantically correct or incorrect) (operation task) and then memorise a neutral to-be-remembered word (storage task) (Fig. 2). All trials consist of a max 10 s response time at sentence presentation, followed by a 500 ms blank screen after which the memorisation words were shown for 800 ms (Klaus

& Schriefers, 2016). The to-be-remembered words were selected using the database of English EMOtional Terms (Grühn, 2016) and the SUBTLEX-NL database (Keuleers et al., 2010). Both experimental sessions included a different list of 20 neutral words, matched for number of syllables (fifty-fifty two and three syllables), concreteness (≤ 4 on a scale of 1: very abstract, to 7: very concrete), emotionality (≤ 3.5 on a scale of 1: neutral, to 7: emotional), and frequency of occurrence in film and television subtitles (2.5–5). Across participants and session, these two lists were assigned in a counterbalanced manner to the neutral and emotional sentence conditions. Importantly, no to-be-remembered/memorisation word started with the same letter as the word in the previous trial.

The task comprised 20 sentence-word pairings in total, 10 trial with neutral sentences and 10 trials with emotional sentences. Incorrect sentences were implemented in half of the trials, leading to 5 correct and 5 incorrect neutral sentences, and 5 correct and 5 incorrect emotional sentences in total (see Supplementary material). Neutral and emotional sentences were presented in blocks of five sentences each. To avoid possible effects of sentence difficulty, half of the sentences were 'long' (i.e., between 10 and 13 words long) and the others 'short' (i.e., less than 10 words long). Neutral and emotional blocks as well as long and short sentences were alternated, with the order counterbalanced across experimental sessions to limit potential presentation-order effects. Trials were separated by 500 ms. Prior to task onset four practice trials were completed.

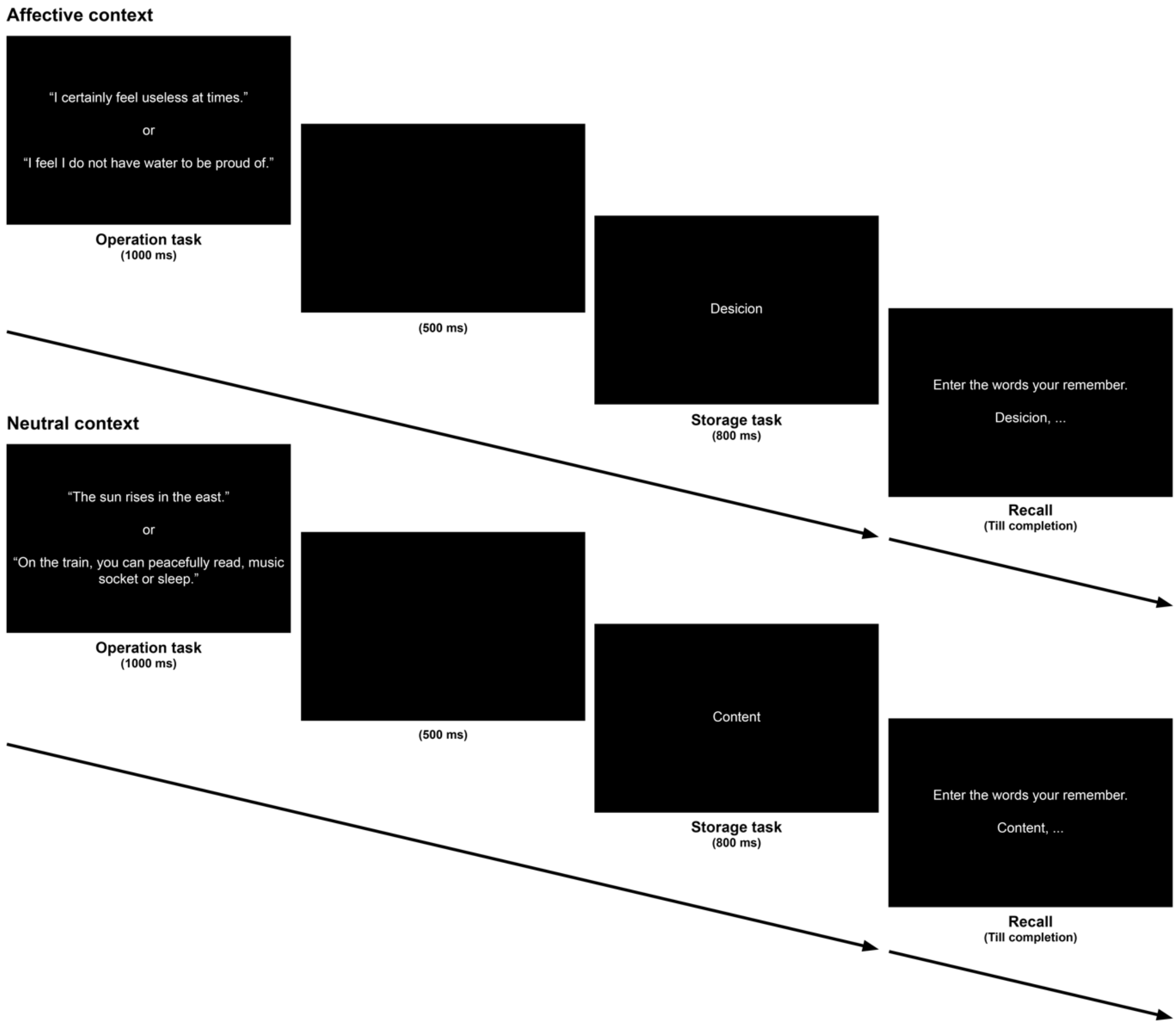
Retrieval stage.

The retrieval stage started approximately 30 minutes after the encoding stage, i.e., after the tACS procedure. Participants were instructed to freely recall the words without time limit, by typing them onto the computer screen.

The measure of interest was span score, i.e., proportion of correctly recalled words.

Figure 2

Emotional Free-Recall Task



Note. Emotional Free-Recall paradigm in English. During the encoding stage of the task participants conduct two tasks per trial: operational (i.e., evaluate a neutral or emotional sentence on semantic correctness) and storage task (i.e., memorise a neutral word). The encoding stage of the memory task is depicted above the left arrow for both contexts.

2.2.3. Subjective measures

To account for interindividual and state-dependent variability in tACS outcomes, participants complete a set of questionnaires at the start of each session (see Supplementary material). Time-point specific measures of individual affective states (i.e., state anxiety) are implemented prior to active or sham tACS. State anxiety is rated with four response options ("Not at all," “Somewhat,” “Moderately so,” and “Very much so”) to statements in the Six-Item State-Trait Anxiety Inventory (STAI-6; Marteau & Bekker, 1992). As individual differences in effort applied to completing the tasks might affect task performance (Feldon et al., 2019; Robinson et al., 2012; Unsworth & Robison, 2020), pre-test task motivation (“How motivated are you to perform well on the following tasks?”) is assessed with responses on a 7-point Likert scale ranging from 1 (“Not motivated at all”) to 7 (“Extremely motivated”) (Hollis et al., 2018). To control for prospective confounding effects of mental fatigue between participants, the Samn-Perelli Fatigue Scale (Samn & Perelli, 1982) is completed prior to and after active or sham tACS, with subjective responses given on a 7-point Likert scale ranging from 1 (“Fully Alert; Wide Awake; Extremely Poppy”) to 7 (“Completely Exhausted; Unable to Function Effectively; Ready to Drop”). At the end of both experimental sessions, tACS sensations and adverse effects are measured using the questionnaire developed by Brunoni and colleagues (2011). Additionally, after the last session, blinding success levels are collected through guessing the stimulation condition and questions concerning stimulation efficacy expectations.

2.3 EEG

Thirty EEG electrodes were applied on the scalp (F3 and F4 missing due to tACS electrode placement, remaining electrodes: Fp1, Fp2, AF3, AF4, F7, F8, Fz, Cz, FC1, FC2, FC5, FC6, C3, C4, CP1, CP2, CP5, CP6, P7, P8, P3, P4, Pz, PO3, PO4, T3, T4, O1, O2 and Oz), according to the International 10–20 EEG system. EEG data was recorded with a BioSemi ActiveTwo system in a sampling rate of 1024 Hz. In addition, facial electrodes were placed on both mastoids, the outer canthus of the left and right eye, and the supraorbital and infraorbital rims of the left eye to detect facial muscle movements (e.g., eye-blink or eye-movement).

2.4. Stimulation protocol

Two rubber electrodes in saline-soaked sponges (3 cm × 3 cm) covered with conductive gel were placed over F3 and F4 (Figure 1B) positions of the International 10–20 EEG system. This tACS electrode montage aims to focus the electric field on the left and right dorsolateral prefrontal cortex (DLPFC), as connectivity in this bifrontal network has been implicated in emotional memory as well as visual memory performance (Klink et al., 2020; Meiron & Lavidor, 2014; Sahu & Tseng, 2021; Weigand et al., 2013). To allow for EEG recording during the stimulation period without the tACS artefacts, frontal tACS is applied using an interleaved tACS-EEG protocol: five blocks of 4-minute stimulation are alternated with 1-minute EEG recording, adding up to a total stimulation time of 20 minutes spread over 25 minutes. The stimulation is applied with an alternating current frequency of 5 Hz and peak-to-peak current intensity of 2 mA. The current is ramped up and ramped down over 15 s at the start and end of the stimulation. To create perceptible control stimulation (i.e., sham tACS condition), participants receive the 15 s ramp-up and 15 s ramp-down active tACS, but without the stimulation in between, during the sham session.

2.5. Analyses

2.5.1. EEG data analyses

Raw EEG data, recorded during the interleaved tACS-EEG procedure, were processed offline with custom MATLAB scripts using EEGLAB v.2022.1 (Delorme & Makeig, 2004) and ERPLAB v.10.0 (Lopez-Calderon & Luck, 2014). In the preprocessing stage, the average EEG signal from the two mastoid electrodes was used for referencing all channels. The raw data was resampled from 1024 Hz to a sampling rate of 256Hz, after which a fourth-order IIR Butterworth filter was implemented for high pass (>0.5 Hz) and low pass (<35 Hz) filtration of low-frequency artifacts (e.g., breathing) and high-frequency noise (e.g., muscle activity). Raw EEG data was then manually inspected and noisy channels were rejected. Eyeblink artifacts were removed by subsequent independent component analysis (Delorme & Makeig, 2004). A total of 298 one-second epochs were generated per session. Noisy epochs in the data were excluded after visual inspection of epochs marked by utilising a semi-automatic artifact rejection method based on the following criteria: max. allowed voltage difference: 150 μV/200 ms; max. allowed absolute amplitude ± 100 μV; max. allowed voltage step of 75 μV/ms (Jung et al., 2000; Rozengurt et al., 2017). On average, 86 of 298 epochs were excluded.

Power spectral density was computed using a fast Fourier Transform approach with Welch's method (Hanning window taper, 50 % overlap). The power spectral density (μV^2/Hz) in the theta band (4-7.5 Hz) and at stimulation frequency (5 Hz) were averaged over epochs and log-transformed.

2.5.2. Statistical methods

A linear mixed effects model was used to determine if the tACS intervention enhances span score and frontal-midline theta EEG power, with within-subject factors of stimulation (active, sham tACS) and state anxiety scores. To ensure robust statistical inference and control nominal Type-I error rates, p-values were estimated based on the Kenward-Roger (KR) correction method. This correction is particularly important in adjusting the degrees of freedom, enhancing the reliability of the estimated effects (Luke, 2017).

Regarding safety, sensations perceived during active and sham tACS were analysed using a MANOVA and followed up with separate t-tests.

3. Results

Demographics

Twenty-seven volunteers (mean age 22.3 years, ranging from 19 to 30 years) participated in our study. Despite random group allocation, women were overrepresented relative to men (F: 20, M: 7) and stimulation order randomisation (active-sham, sham-active tACS) was skewed.

During the first session, 19 participants received active tACS, while only 9 received sham tACS. Due to time constraints, we could not include the fully a-priori computed sample size in the current analysis. Regarding simulation order randomisation there was no significant difference in sex (x^2(1, 27) = 3.4835, *p* = .06) or age (*F*(1,52) = 2.324, *p* = .133). Subjective ratings of tiredness (*t*(26) = -1.19, *p* = .24) and motivation (*t*(26) = .22, *p* = .82) were comparable at the start of the every active and sham tACS session. State anxiety scores significantly differed at the start of active and sham tACS sessions (*t*(26) = 2.05, *p* = .05).

Safety and blinding

The stimulation intervention was well tolerated. Sensations perceived during active or sham tACS significantly differed *(F*(12,41) = 4.111, *p* < .001). While itchiness, pain, burning and heat sensation on the skin underneath electrode location were detected to a significantly stronger extent in the real tACS condition compared to the sham condition, the mean occurrence of these sensations is relatively low (i.e., scored below "moderate") (Table 1). Participants correctly identified stimulation condition significantly above what could be attributed to chance (Table 2). Twenty-five individuals (93%) were able to correctly determine in which experimental session active or sham tACS was administered.

Table 1

Summary of the sensations perceived during the active and sham tACS condition

	Active tACS		Sham tACS		*t(26)*	*p*
	M	*SD*	*M*	*SD*		
Sensations						
Itchiness	.89	.64	.37	.56	3.0	.006*

Pain	.59	.64	.15	.36	4	< .001*
Burning	1.00	.68	.26	.53	5.0	< .001*
Electrode heat	.41	.64	.11	.42	2.3	.030*
Metallic taste	.04	.19	0	0	1	.327
Tiredness	1.52	.89	1.59	.97	-.4	.722
Headache	.52	.80	.44	.58	.4	.678
Neck pain	.33	.68	.30	.54	.4	.663
Seeing flashes of light	.26	.81	.07	.27	1.5	.134
Dizziness	.07	.27	.15	.36	-1.4	.161
Nausea	.07	.27	0	0	1.4	.161
Concentration difficulties	1.19	.96	1	.88	1	.327

Note. Perceived sensations during active and sham tACS as measured on a 5-point Likert Scale (0 = "none", 1 = "slight", 2 = "moderate"; 3 = "intense", 4 = "unbearable"). $P \leq 0.05$* are defined as statistically significant.

Table 2

Summary of the blinding rates of the experimental procedure

	Active tACS	Sham tACS
Correct guess rate	92%	92%
Confidence rate	80%	77%

Note. Assessment of blinding success entailed participants guessing whether they received active or sham tACS. The confidence ratings to their judgement (0-100 scale, *0% = "not at all"; 100% = "absolutely sure"*) are also reported.

Frontal-midline theta power

For frontal-midline EEG theta power at theta-band frequencies (4-7.5 Hz), no significant main effect of *Stimulation* appeared (*KR adjusted p* = .53; *β* = .02, *SE* = .03) (Figure 3). Moreover, no significant main effect for *State Anxiety scores* (*KR adjusted p* = .71; *β* = .01, *SE* = .02) or *Stimulation* × *State Anxiety scores* interaction effect (*KR adjusted p* = .99; *β* = -.00, *SE* = .02) was found, indicating that state anxiety levels did not affect tACS efficacy.

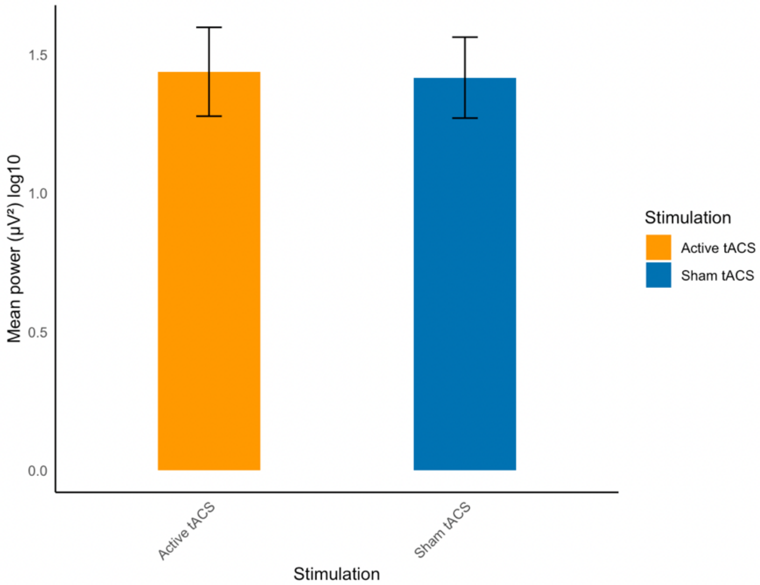


Figure 3. Mean frontal-midline theta power per stimulation condition. Depiction of mean frontal-midline theta power for active and sham tACS stimulation condition. Error bars represent standard deviation of the mean.

Span score

For span score, no main effect of *Stimulation* was detected (*KR adjusted p* = .09; *β* = -.17, *SE* = .09) (Figure 4). Moreover, the main effect of *State Anxiety scores* and the *Stimulation* × *State Anxiety* interaction effect was not significant (*State Anxiety scores*: *KR adjusted p* = .81; *β* = .02, *SE* = .07; *Stimulation x State Anxiety scores*: *KR adjusted p* = .48 *β* = -.06, *SE* = .08).

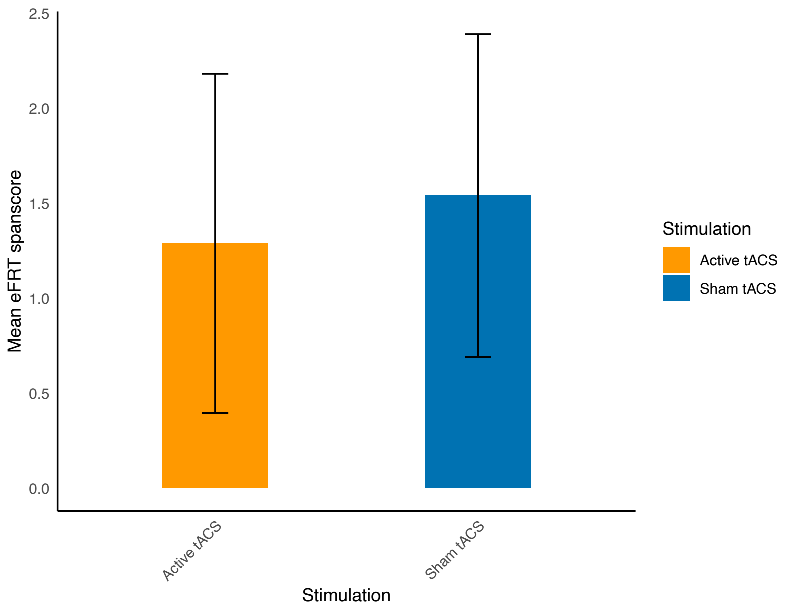


Figure 4. Mean span score per stimulation condition. Depiction of mean emotional Free-Recall Task span score for active and sham tACS stimulation condition. Error bars represent standard deviation of the mean.

4. Discussion

Intrusions, a prominent symptom of PTSD, appear to occur when cognitive resources are employed to cope with trauma-related content instead of being directed toward current goal completion. In the present study, we investigated whether theta tACS could enhance recall performance through facilitation of memory consolidation, as increased neural oscillations within this frequency have been linked to this memory process (Rozengurt et al., 2017). The effect of theta tACS was evaluated by performance on a free-recall task where to-be-remembered stimuli were presented during an interfering task. Contrary to our hypothesis, the results showed no significant increase in frontal-midline theta power during active theta tACS over the left and right dorsolateral prefrontal cortex, as measured in an interleaved tACS-EEG procedure. No support was found either for a difference between active v. sham theta tACS on free-recall performance. Hence, despite previously reported positive effects of tACS on memory (e.g., Alekseichuk et al., 2016; Jaušovec & Pahor, 2017; Pahor & Jaušovec, 2018; Polanía et al., 2012; Sahu & Tseng, 2021), our results do not support the enhancement of memory consolidation after interference by frontal tACS in healthy individuals. Collectively, these results prompt considerations on why theta tACS did not provide an effect on recall performance, and whether there are alternative means to successfully modulate memory with non-invasive brain stimulation.

Ceiling effects and individual variability

The lack of tACS effects on frontal theta power and recall performance in this study may have several explanations, including the potential ceiling effects non-personalised approach of stimulation. Whether tACS can modulate the frequency of an ongoing brain oscillations (i.e., entrain oscillations) depends on stimulation frequency and amplitude (Antal & Paulus, 2013; Maiella et al., 2022). TACS matched to the endogenous frequency allows weak stimulation amplitudes to entrain endogenous oscillations (Ali et al., 2013). Conversely, stimulation frequencies deviating from the endogenous frequency only cause increased oscillation power when these endogenous oscillations have a relativity high amplitude (Alagapan et al., 2016; Antal & Herrmann, 2016; Schimdt et al., 2014). Absence of any significant effect on theta power might be due to ceiling effects of theta activity; that is, if the brain produces theta oscillations as part of its natural processes (e.g., high theta amplitudes during memory consolidation; Neuling et al., 2013) the use of weak theta stimulation in turn could have prevented further increase in theta amplitude. To modulate memory-related processes, tACS studies have typically used mid-band frequencies across all subjects (e.g., 5 Hz for theta-band (4-7.5 Hz) stimulation (Bjekić et al., 2022; Schutter & Wischnewski, 2016; Senoussi et al., 2022). However, studies using EEG recordings to determine individual peaks within this frequency spectrum suggest that tACS efficacy indeed relies on the ongoing oscillatory state (Feurra et al., 2011). Moreover, interindividual differences in such theta peaks are linked to variable performance on cognitive tasks (Neuling et al., 2013). The use of a frequency band average approach to brain stimulation has provided inconsistent findings, suggesting that indeed intra- and inter-individual variability in theta activity might strongly influence effectivity of theta tACS at a set frequency (De Koninck et al., 2021). For instance, Aktürk et al. (2022) assessed cognitive aftereffects of a theta tACS protocol using individual peak frequencies of theta-band oscillations across participants. In this study, slowing down individual theta frequency (ITF), by administering theta stimulation 1 Hz below the personal theta peak, resulted in enhanced performance on a visual working memory task. This finding may be explained by the facilitation of gamma-band activity at a preferred theta phase (Köster et al., 2019). High gamma amplitudes are suggested to be associated with the early phase of the theta oscillation (0°–90°; i.e., the first quarter of a complete theta cycle), corresponding to the onset of a stimulus (Clouter et al., 2017). Slowing down the ITF may have affected the timing and width of the theta peak and thereby may have enhanced the synchronisation of neural firing, creating a window of heightened excitability. Theta-gamma phase-amplitude coupling is assumed to facilitate the integration of perceptual information into existing networks (e.g., prefrontal cortex-hippocampus axis) (Buzsáki, 1996; Paßmann et al., 2023). In contrast, stimulation at ITF increased theta power and thus led to entrainment effects, but not to cognitive enhancements (Aktürk et al., 2022). In our study, the stimulation frequency was not adjusted to individual theta peak frequencies, which may have reduced the efficacy of tACS-induced changes in theta power. Thus, future research could benefit from stimulating at the specific individual theta frequency.

Electrode configuration

While previous research provides evidence for a beneficial effect of tACS on memory, inconsistencies among comparable studies and null results cast doubts on the robustness of this technique. TACS applied to the frontal or parietal lobe are among the prominent areas stimulated as these seem implicated in underlying biological mechanisms of memory. Pohar and Jaušovec (2018) extensively investigated which specific tACS parameters might be more suited for visual working memory enhancement. In their study four experiments were conducted with differential electrode configurations (i.e., bi-frontal, bi-parietal, left fronto-parietal, and right fronto-parietal) and individually determined theta frequency stimulation. Although bi-parietal and right fronto-parietal ITF stimulation significantly increased theta power, inhibition and memory interference tests showed no significant improvement. No effect of tACS on EEG spectral theta power or behavioural measures was found for bi-frontal and left fronto-parietal stimulation, suggesting that stimulation including at least one electrode targeting the parietal areas might elicit the proposed behavioural effects (Jaušovec & Jaušovec, 2014; Jaušovec, Jaušovec & Pahor, 2014; Pahor & Jaušovec, 2014). Further highlighting the importance of examining optimal stimulation parameters, mid-band theta (6 Hz) tACS of the left frontal-parietal network did elicit improvements in overall reaction time on a similar visual working memory task (Polanía et al., 2012). A study by Alekseichuk and colleagues (2020) showed that right but not left parietal theta tACS augmented associative memory performance. Accordingly, studies targeting parietal areas show an effect of tACS, suggesting that parietal electrode montages are more effective in modulating memory processes with tACS. Hence, the focus on bi-frontal stimulation in our study might have limited any tACS effect on theta amplitude and cognitive enhancement.

Conclusion

Our findings provided no evidence for bi-frontal theta (5 Hz) tACS effects on oscillatory theta power or free-recall memory performance. The used stimulation parameters (i.e.., non-personalised mid-band frequency stimulation and bi-frontal electrode montage) may explain this lack of effect. Future studies are needed to investigate the potential advantages associated with personalised stimulation methodologies and alternative electrode montages. The comprehensive insights derived from the present study may contribute to the refinement of tACS protocols for enhancing memory processes.

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Appendix. Supplementary information

Supplemental Figures and Tables

Table S1

	Active tACS	Sham tACS
Correct guess rate	92%	92%
Session 1	94%	89%
Session 2	89%	94%
Confidence rate	80%	77%
Session 1	78%	76%
Session 2	81%	77%

Note. Average accuracy scores of stimulation type (active or sham tACS) detection following session 2.

Table S2

	M	*SD*
Active tACS		
Task performance	.5	.5
Mental state	.2	.4
Sham tACS		
Task performance	.2	.4
Mental state	.1	.2

Note. Participants' estimated effect of stimulation on behavioural and psychological measures in each experimental condition. Mean values vary from 0 ("no effect") no 1 ("effect"). Effects of stimulation are assigned a value of 1, irrespective of direction. On average, subjects reported no perceived effect of active and sham tACS.

Supplemental Experimental Procedures
Questionnaires
End of session questionnaire

What is your subject number?

____

Which session is this (1st or 2nd session)?

- ◯ Session 1
- ◯ Session 2

How tired are you?

Completely exhausted, unable to function	Extremely tired, difficult to concentrate	Moderately tired	A little tired	Okay, reasonably fresh	Very lively, not at peak level	Fully alert, wide awake
◯	◯	◯	◯	◯	◯	◯

Q1 Did you experience something special during stimulation?
Use the scale to answer the following questions regarding different sensations and the degree to which you felt them:

Q2 To what extent did you experience:

	none	slight	moderate	intense	unbearable
Itchiness	○	○	○	○	○
Pain	○	○	○	○	○
Burning sensation	○	○	○	○	○
Heat under electrodes	○	○	○	○	○
Metallic taste	○	○	○	○	○
Tiredness	○	○	○	○	○
Headache	○	○	○	○	○
Neck pain	○	○	○	○	○
Seeing flashes of light	○	○	○	○	○
Dizziness	○	○	○	○	○
Nausea	○	○	○	○	○
Concentration difficulties	○	○	○	○	○

The following questions were only answered when indicated that this was the last questionnaire in experimental procedure, i.e., during session 2.

Q1 Indicate when you believe you received real stimulation or placebo stimulation (sham stimulation):

	Real stimulation	Placebo stimulation
During the first session	○	○
During the second session	○	○

Q2 How sure are you of your choice?
0% = not at all; 100 % = absolutely sure

	0 10 20 30 40 50 60 70 80 90 100
session 1	
session 2	

Q3 Which general effect did you expect real stimulation would have on someone's *task performance*?

○ The performances become faster/better

○ The performances become slower/worse

○ No effect on the performances

Q4 Which general effect did you expect real stimulation would have on someone's *mental state*?

○ The mental state becomes better

○ The mental state becomes worse

○ No effect on the mental state

Q5 Do you think stimulation has affected your *task performance*?

	yes, my performance became faster/better	yes, my performance became slower/worse	no
Session 1	○	○	○
Session 2	○	○	○

Q6 Do you think stimulation has affected your *mental state*?

	yes, my mental state became faster/better	yes, my mental state became slower/worse	no
Session 1	○	○	○
Session 2	○	○	○

Behavioural task and stimuli

Table S3

	Word list A	Word list B
Three syllables	Bestemming	Bedoeling
	Beweging	Beschrijving
	Ervaring	Conditie
	Gedachte	Energie
	Gegevens	Gewoonte
	Methode	Oplossing
	Omgeving	Principe
	Theorie	Privacy
	Verveling	Routine

	Verzonnen	Tenminste
Two syllables	Belang	Afstand
	Eeuwen	Geduld
	Fase	Inhoud
	Grenzen	Moment
	Kennis	Oorzaak
	Kwestie	Raadsel
	Pardon	Ritme
	Proces	Systeem
	Rechten	Uitspraak
	Toeval	Visie

Note. Three- and two-syllable words presented in the emotional Free-Recall Task. Words selected, and translated to Dutch if needed, from the database of English EMOtional TErms (Grühn, 2016) and the SUBTLEX-NL database (Keuleers et al., 2010).

Table S4

Condition	Sentence list A	Sentence list B
Neutral		
Correct	"Een cirkel heeft geen begin of einde"	"Een hond kwispelt vaak met zijn staart"
	"De zon gaat elke dag op en onder"	"De zon komt op in het oosten"
	"Een pen kan inkt op papier achterlaten"	"Groenten zijn gezond om te eten"
	"Een boom verliest in de herfst zijn bladeren en wordt kaal"	"In de lente groeien er veel bloemen en planten in de natuur"

	"Het lichaam heeft voldoende water nodig voor een goede werking"	"Een vis kan goed zwemmen en ademhalen onder water"
Incorrect	"In een museum kun je boodschappen doen"	"Boeketten bevatten veel tafels"
	"Een fiets is een knop vervoersmiddel"	"De trap draait rond de zon"
	"Dieren hebben verschillende soorten agenda nodig om te overleven"	"Bomen produceren zuurstof door ademhaling"
	"In de trein kun je rustig lezen, muziek stopcontact of slapen"	"Een spelt kan je warm houden op een koude winterdag"
	"Een hond is een trouw huisdier dat vaak wordt doorstreept"	"Bij het kamperen slaap je in een auto en leef je in de folder"
Emotional		
Correct	"Anderen doen dingen beter dan ik"**	"Ik faal vaak bij de dingen die ik doe"**
	"Ik ben boos op mezelf om wie ik ben"**	"Ik voel me minderwaardig"**
	"Ik voel me soms nutteloos"***	"Ik ben bang dat ik stom overkom bij anderen"**
	"Als ik meer kon zijn als anderen, dan zou ik me beter voelen"**	"Ik wou soms dat ik kon verdwijnen als ik bij anderen ben"**
	"Over het algemeen heb ik de neiging mij een mislukkeling te voelen"***	"Ik heb het gevoel dat ik niet veel heb om trots op te zijn"***

Incorrect	"Ik rijd me minderwaardig"**	"Ik schaam me voor sla"**
	"Ik ben bang dat ik stom computer bij anderen"**	"Ik ben boos op mezelf om telefoon ik ben"**
	"Soms denk ik dat ik nergens aardbei voor ben"***	"Ik plant dat er met mij gesold wordt"
	"Ik wou soms dat ik kon verdwijnen als ik bij datum ben"**	"Ik heb het gevoel dat ik niet water heb om trots op te zijn"***
	"Als ik me rot voel, heb ik het idee dat de meeste andere mensen muis zijn dan ik"*	"Ik loop afkeurend en oordelend tegenover mijn eigen tekortkomingen"*

Note. Neutral and emotionally negative, semantically (in)correct sentences presented in the emotional Free-Recall Task. Sentences adapted from the Dutch translations of the Self-Compassion Scale–Short Form (Raes et al., 2011)*, the Self-Esteem Rating Scale-Short Form (Lecomte et al., 2006)**, and the Rosenberg Self-Esteem Scale (Franck et al., 2008)***.