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Effects of transcranial direct current stimulation over the posterior parietal cortex on episodic memory reconsolidation

Margot Crossman[1], Gergely Bartl[1], Rebecca Soerum[1], and Marco Sandrini[1*]

[1] Department of Psychology, University of Roehampton, London SW15 4JD, UK

*Correspondence to:

Marco Sandrini, PhD

Department of Psychology

University of Roehampton

Whitelands College

Holybourne Avenue

London, UK

SW15 4JD

email: marco.sandrini@roehampton.ac.uk

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Abstract

Consolidated memories may return to labile/unstable states after their reactivation, thus requiring a restabilization process that is known as reconsolidation. During this time-limited reconsolidation window, reactivated existing memories can be strengthened, weakened or updated with new information.

Previous studies have shown that non-invasive stimulation of the lateral prefrontal cortex after memory reactivation strengthened existing verbal episodic memories through reconsolidation, an effect documented by enhanced delayed memory recall (24h post-reactivation). However, it remains unknown whether the left posterior parietal cortex (PPC), a region involved during reactivation of existing episodic memories, contributes to reconsolidation.

To address this question, in this double-blind experiment healthy participants (n=27) received transcranial direct current stimulation (tDCS) with the anode over the left PPC after reactivation of previously learned verbal episodic memories. Memory recall was tested 24h later. To rule out unspecific effects of memory reactivation or tDCS alone, we included two control groups: one that receives tDCS with the anode over the left PPC without reactivation (n=27) and another one that receives tDCS with the anode over a control site (primary visual cortex) after reactivation (n=27). We hypothesized that tDCS with the anode over the left PPC after memory reactivation would enhance delayed recall through reconsolidation relative to the two control groups.

No significant between groups differences in the mean number of words recalled on day 3 occurred, suggesting no beneficial effect of tDCS over the left PPC.

Alternative explanations were discussed, including efficacy of tDCS, different stimulation parameters, electrode montage, and stimulation site within the PPC.

1. Introduction

The process that transforms the encoding of new information into long-term memory is known as memory consolidation. According to the consolidation model memories are in a labile/unstable phase (i.e., vulnerable to interference) for a limited time after encoding, but as time passes, memories stabilize and become resistant to interference (McGauth, 2000). However, accumulating evidence has demonstrated that consolidated memories can return to a labile/unstable phase when they are reactivated during retrieval or through reminder cues. The process that restabilizes the existing memories after reactivation is known as memory reconsolidation (Alberini & LeDoux, 2013; Nader & Hardt, 2009; Sandrini, Cohen, & Censor, 2015; Schwabe, Nader, & Pruessner, 2014). During this time-limited reconsolidation window, reactivated memories can be changed. Thus, memories can be strengthened, weakened or updated with new information (Agren, 2014; Forcato, Fernandez, & Pedreira, 2014; Lee, Nader, & Schiller, 2017; Sandrini et al., 2015). Prediction error, a mismatch between expected and current events, has been suggested as a requirement to destabilize memories and make them vulnerable to modification (Fernández, Boccia & Pedreira, 2016; Sinclair & Barense, 2018).

Most reconsolidation work has been conducted in animal models because this allows the use of invasive methods such as the injections of protein synthesis inhibitors into brain areas to interfere with the neural processes underlying memory (e.g., Nader, Schafe, & LeDoux, 2000). However, noninvasive brain stimulation techniques (Dayan, Censor, Buch, Sandrini, & Cohen, 2013; Parkin, Ekhtiari, & Walsh, 2015; Polania, Nitsche, & Ruff, 2018), such as repetitive Transcranial Magnetic Stimulation (rTMS) and transcranial Direct Current Stimulation (tDCS), provide a safe approach to change reactivated memories

through reconsolidation (Sandrini et al., 2015). Based on stimulation parameters (e.g. frequency for TMS or polarity for tDCS) and the initial neural activation state of the stimulated region, these techniques can enhance or impair behavioral performance. These facilitation or interference effects allow researchers to establish a causal link between a cortical region and a cognitive function.

Episodic memory refers to the recall of specific details about past events (Tulving, 1983). Clinical work has shown that this type of declarative long-term memory relies on the integrity of the medial temporal lobe (MTL), which includes the perirhinal, entorhinal parahippocampal cortices, and the hippocampus (Dickerson & Eichenbaum, 2010; Eichenbaum, 2004; Shimamura, 1995; Squire, 1992). In addition, it has been shown that the prefrontal cortex (PFC) and MTL–PFC interactions are important for episodic memory (Bilek et al., 2013; Eichenbaum, 2017; Manenti, Cotelli, Robertson, & Miniussi, 2012; Simons & Spiers, 2003; Szczepanski & Knight, 2014). There is also evidence supporting the functional involvement of the posterior parietal cortex (PPC) during encoding and retrieval of episodic memories (Berryhill, 2012; Cabeza, Ciaramelli, & Moscovitch, 2012; Cabeza, Ciaramelli, Olson, & Moscovitch, 2008; Rugg & King, 2017; Rugg & Vilberg, 2013; Sestieri, Schulman, & Corbetta, 2017; Spaniol et al., 2009; Uncapher & Wagner, 2009; Wagner, Shannon, Kahn, & Buckner, 2005).

Regarding the role of PPC in encoding, there is evidence that the formation of episodic memories is affected by attention (Chun & Turk-Browne, 2007; Craik, 2001). According to the dual-attention perspective (Corbetta & Shulman, 2002; Corbetta, Patel, & Schulman, 2008), dorsal PPC mediates goal-directed or ‘top-down’ attention, whereas ventral PPC

mediates stimulus-driven or 'bottom-up' attention. A review of functional neuroimaging studies of PPC has revealed the effects of activation of the ventral and dorsal systems on encoding (Uncapher & Wagner, 2009). The authors showed that the positive subsequent memory effects are mainly observed in dorsal PPC associated with goal-directed attention, while all negative subsequent memory effects are mainly observed in ventral PPC associated with stimulus-driven attention. These findings suggest that various parietal attentional mechanisms modulate episodic memory encoding.

Regarding the role of PPC in retrieval, fMRI studies have shown that successful episodic memory retrieval is mainly associated with activity in the left inferior PPC. A review of neuropsychological, TMS and neuroimaging findings supports early proposals (Rugg & Vilberg, 2013; Shimamura, 2011; Wagner et al., 2005) that the inferior PPC may contribute to the representation of retrieval episodic information (Rugg & King, 2017). A review by Sestieri, Shulman and Corbetta (2017) provides a complementary view to the one presented by Rugg and King (2017). Based on functional neuroimaging findings, the authors proposed a functional-anatomical model of the involvement of PPC in memory retrieval. These findings suggest dynamic interactions, potentially mediated by frontal regions, between different PPC regions involved in perceptual attention and episodic memory.

So far, only a few studies investigated the neural substrates of episodic memory reconsolidation. Sandrini, Censor, Mishoe, and Cohen (2013) used repetitive TMS (rTMS) to determine the causal role of the right dorsolateral PFC (DLPFC), a brain region involved during retrieval (Sandrini, Cappa, Rossi, Rossini, & Miniussi, 2003) or reactivation of existing episodic memories (Diekelmann, Büchel, Born, & Rasch, 2011). The results showed that rTMS to the right DLPFC after memory reactivation strengthened existing

verbal episodic memories, an effect documented by enhanced memory recall (24h post-reactivation) relative to control groups that received rTMS to the right DLPFC without reactivation or rTMS to a control site (vertex) after reactivation (Sandrini, et al., 2013). Similar findings have been reported using tDCS with the anode over the left lateral PFC in young and older adults (Javadi & Cheng, 2013; Manenti et al., 2017; Sandrini et al., 2014). Other studies used fMRI to investigate the neural substrates of this memory process. Schwabe, Nader, Wolf, Beaudry, and Pruessner (2012) showed that the administration of propranolol, a beta blocker, during reactivation reduced subsequent memory for emotional pictures, and decreased activity in the amygdala. Forcato et al. (2016) revealed a differential activation of the left hippocampus only during the presentation of a reminder that effectively triggered the labilization-reconsolidation process. Simon, Gómez, Nadel, and Scalf (2017) found that high levels of prediction error, as showed by activity in the temporoparietal junction (TPJ), resulted in a new memory formation, and low levels led to updating of the original memory. St. Jacques, Olm, and Schacter (2013) examined the neural substrates of reactivation-induced updating that enhance and distort memories for events experienced during a museum tour. During fMRI (48h later), target photographs were used to reactivate memories from the tour followed by a novel lure photograph from an alternate tour. During the recognition memory task (48h after fMRI), participants were presented with target and lure photographs they saw during fMRI. The behavioral results showed that reactivation enhanced memory for targets, but also facilitated encoding of the lures that followed reactivated targets. The fMRI results revealed that the quality of reactivation, as indexed by an individual subjective feeling of recollection, modulated subsequent true and false memories effects through the common recruitment of the left

posterior parahippocampal, bilateral retrosplenial, and bilateral posterior inferior parietal cortices, a subset of retrieval-related brain regions (Ranganath & Ritchley, 2012). In addition, unrelated to the quality of reactivation, there were some differences in neural recruitment associated with these subsequent effects. Subsequent true-memory effects were associated with greater recruitment of left frontoparietal control regions (i.e. DLPFC and PPC) during the target versus lure presentation. Subsequent false-memory effects showed less involvement of frontoparietal control regions and greater engagement of bilateral temporal cortices, which some studies have associated with conceptual processes that contribute to the formation of false memories (Dudai, 2012). This study shows that, depending upon neural recruitment during reactivation, existing memories can be strengthened or integrated with novel information.

Although this study suggests that the left PPC may contribute to the strengthening of existing episodic memories through reconsolidation, the causal role of the left PPC region in this memory process still remains unknown.

The aim of this pre-registered double-blind experiment was to investigate the causal role of left PPC in episodic memory reconsolidation. Specifically, our goal was to determine whether modulation of the left PPC through tDCS (anode over the left PPC and cathode over vertex) after memory reactivation would strengthen existing memories through reconsolidation. Considering the role of hippocampus in contextual reconsolidation (Debiec, LeDoux, & Nader, 2002; Morris et al., 2006) and the idea that tDCS acts by modulating functional connectivity (Krause et al., 2017; Keeser et al., 2011), tDCS applied with the anode over the left PPC after memory reactivation might strengthen the functional

connectivity between this cortical region and the hippocampus (Mesulam, Van Hoesen, Pandya, & Geschwind, 1977; Cavada & Goldman-Rakic, 1989, Kahn, Andrews-Hanna, Vincent, Snyder, & Buckner, 2008; Wang et al., 2014). Variations in the strength of links between hippocampus and neocortex are at the heart of different studies in the field of memory consolidation (Dudai, 2012).

We choose to apply this neuromodulation technique over the left PPC for the following reasons: 1) tDCS can be useful to determine the contribution of left PPC to episodic memory reconsolidation because there is no a priori hypothesis that a specific region within the left PPC is associated with reconsolidation of verbal epsiodic memories; 2) tDCS applied with the anode over the left DLPFC strengthened existing episodic memories in young and older adults (Javadi & Cheng, 2013; Manenti et al., 2017; Sandrini et al., 2014); 3) fMRI studies have shown the involvement of left PPC, a component of a well-established cortical-hippocampal network (Ranganath & Ritchey, 2012), during memory retrieval (Wagner et al., 2015; King & Rugg, 2017; Rutishauser, Aflalo, Rosario, Pouratian, & Andersen, 2018) or reactivation of existing memories (St. Jacques et al., 2013).

In this double-blind experiment there were three sessions on consecutive days (Sandrini et al., 2013). On Day 1, participants learned a list of 20 words (at least 17/20 words or until a maximum of 4 learning trials). On Day 2 (24h later), existing memories were reactivated using a contextual reminder (without explicit recall), and 10 minutes later tDCS was applied with the anode over the left PPC. Memory recall was tested on Day 3 (24h post-reactivation). To rule out unspecific effects of memory reactivation or tDCS alone, we included two control groups: one that receives tDCS with the anode over the left PPC without reactivation and another one that receives tDCS with the anode over the primary

visual cortex (control site) after reactivation.

We hypothesized that tDCS applied with the anode over the left PPC after memory reactivation would enhance delayed recall (i.e. words from the list learned on Day 1) through reconsolidation relative to the two control groups.

The findings of this investigation are likely to have significant implications for models of the neural basis of reconsolidation in humans. A better understanding of memory reconsolidation may help develop effective interventions to modulate existing memories in patients with memory disorders.

2. Materials and Methods

2.1 Statistical power analysis and sample size estimation

In our sample size calculation we considered non-invasive brain stimulation studies which investigated the role of PFC in episodic memory reconsolidation using a similar methodology to the current experiment (i.e. studies applying rTMS or tDCS and employing a verbal recall task, Sandrini et al., 2013, Sandrini et al., 2014). Improved recall was found by Sandrini et al. (2013) with rTMS (η^2=0.654) and Sandrini et al. (2014) with tDCS (η^2=0.431), all using similar control conditions to those proposed in the current experiment. Given the novel nature of our inquiry (i.e. looking at the effect of bilateral tDCS on reconsolidation) and the high available effect size point estimate (η^2=0.431, η^2=0.654) from these studies with low sample sizes, we adopted a more conservative measure in order to retain power in case of smaller population effects. Thus, we calculated sample size for one-way analysis of variance (ANOVA) for independent samples using a lower, η^2=0.14 estimate (conventionally accepted as a large effect). Using the open-source G*Power

statistical software version 3.1.9.2 (Faul, Erdfelder, Lang, & Buchner, 2007) we determined that a total sample necessary to detect a similar-sized effect with a power of α=.05 and β=.9 is N=81.

2.2 Participants

As informed by the power analyses, N=81 healthy and native English-speaking volunteers (between 18 and 35 years old) were recruited from the student and general population to participate in three experimental sessions.The Stage 1 protocol was accepted in principle on 14 September 2018 and can be accessed at https://osf.io/akmwn/. Eighty-seven participants were enrolled in the study and eighty-one completed all the three sessions (60 F and 21 M). The mean age was 20.86 and the standard deviation was 2.91.

All participants will have corrected-to-normal or normal vision, will be right-handed according to the Edinburgh Handedness Inventory (LI > 75; Oldfield, 1971).

Prior to taking part, all participants were asked to complete a screening questionnaire for transcranial electrical stimulation (Antal et al., 2017). Exclusion criteria were pregnancy, brain injuries, neurological or psychiatric disorders, current medication affecting the central nervous system, metal implants, skin problems on the head, history of seizures, pacemakers.

In agreement with Declaration of Helsinki and approved by the Ethical committee of the University of Roehampton, participants signed an informed consent and received monetary or course credit compensation for attending the three experimental sessions.

Replacement participants were recruited in cases when participants dropped out of the study, when there were technical problems (e.g., failure to achieve electrode impedance

below a cutoff of 15kΩ, automatic abortion of stimulation for unexpected sudden movements and impedance increases), or when immediate recall performance after the last learning trial (Day 1) was less than 2.5 standard deviation from the mean of the group.

2.3 Transcranial direct current stimulation (tDCS)

tDCS is a portable device which uses a constant low-intensity current (between 1 and 2 mA) delivered directly to the cortex via surface electrode pads, anode and cathode (Dayan et al., 2013; Woods et al., 2016). tDCS applied with the anode over the primary motor cortex (M1) generally increases cortical excitability as assessed by Motor evoked Potentials induced by TMS, whereas tDCS applied with the cathode over M1 generally decreases cortical excitability (Nitsche et al., 2008).

A Neuroconn DC stimulator (NeuroCare Group Gmbh, Munchen, Germany) was used to administer current to the brain. The tDCS stimulator was set to administer 1.5 mA for 20 minutes with a ramp time of 20 seconds. Electrode size was 5x5 cm^2 for the anode and 7x8 cm^2 for the cathode. The current density was maintained below safety limits (Bikson et al., 2016). When one electrode is larger than the other one, the current density is smaller on the larger electrode, producing neuromodulation mainly under the smaller (Nitsche et al., 2007). To reduce contact impedance, sponges encasing the rubber electrodes were soaked in saline.

In the PPC stimulation groups (PPC-reactivation (PPC-R); PPC-no reactivation (PPC-NR)), the anode was placed over CP5 according to the 10–20 EEG international electrode scalp positioning system (Jasper, 1958). It has been shown that the main target region for C5 is the left inferior parietal lobule/TPJ region (Herwig, Satrapi, & Schonfeldt-Lecuona,

2003). The cathode was placed over the vertex (Cz), with the 8cm side of the pad parallel to the line from ear to ear. Vertex is commonly considered a neutral stimulation site (Sandrini et al., 2015).

Computer simulations conducted using tDCS Targets software (Soterix Medical, New York, NY) suggests that this montage successfully targets the left PPC (see Figure 1).

In the primary visual cortex reminder group (V1-R), the anode was positioned over 10–20 location Oz. The cathode was centered on the vertex (Cz).

INSERT FIGURE 1 ABOUT HERE

2.4 Procedure and experimental task

This double-blind experiment consisted of three sessions on consecutive days, as in a previous reconsolidation study (Sandrini et al., 2013): Day 1 (learning session), Day 2 (reminder or not and tDCS), and Day 3 (free recall test). Participants were randomly assigned to one of three experimental groups (n=27 in each group): PPC-reminder (PPC-R), PPC-no reminder (PPC-NR), V1-Reminder (V1-R). PPC-NR and V1-R will serve as control groups (see Figure 2). Participants were informed that they have to memorize a list of words and that on the second day they receive 20 min. of tDCS. No information were given to participants regarding the third day.

To achieve effective blinding, the experimenter present during the learning phase (Day 1) and tDCS session (Day 2) was not involved during the testing phase (Day 3).

INSERT FIGURE 2 ABOUT HERE

On Day 1 (learning session), participants were asked to learn a list of 20 words of similar length with higher levels of concreteness and imageability (see Appendix A), chosen from the MRC Psycholinguistic Database (Coltheart, 1981). This procedure was repeated until the participants recall at least 17 of the 20 words (85%) or until a maximum of four learning trials is reached, as in a previous reconsolidation study (Sandrini et al., 2013). The experimenter pulled out one item at a time at random (a word printed on piece of card) from a white bag. Participants were asked to read each word, to pay close attention so they can remember the words later and to place them in a blue bag. When all 20 words have been placed into a blue bag, the experimenter took away this bag and asked the participants to recall as many words as possible. Before the next learning trial, the words were replaced in the white bag and mixed. At the end of this session participants were asked to complete a memory strategies questionnaire (Manenti, Cotelli, Calabria, Maioli, & Miniussi, 2010), which comprises 12 possible strategies that can be used to enhance the learning or encoding of information. Participants rate how often they have used each strategy during the learning task using a 5-point-scale (0, never; 1, rarely; 2, sometimes; 3, often; and 4, always). The total score ranges between 0 and 52.

On Day 2 (24 hours after the learning session), the procedure differed for the three experimental groups.

For the PPC-R and V1-R groups, the same experimenter of Day 1 showed to the participants the empty blue bag and ask, “Do you remember this blue bag and what we did with it yesterday?” Participants were encouraged to describe the procedure but were stopped if they started to recall any specific words. On the basis of previous findings

showing that the reconsolidation process seems to begin between 3 and 10 min after memory reactivation (Monfils, Cowansage, Klann, & LeDoux, 2009), tDCS was applied 10 minutes after the contextual reminder (Sandrini et al., 2013, Sandrini et al., 2014). It has been shown that existing episodic memories are automatically reactivated if the original spatial context (i.e. same experimental room of Day 1) is part of the reminder (Hupbach, Hardt, Gomez, & Nadel, 2008; Sandrini et al., 2013). In addition, a recent meta-analysis showed evidence for reactivation-induced changes in human episodic memory (Scully, Napper, & Hupbach, 2016).

Since V1 is not part of the brain network specialized for episodic memory, inclusion of an active control stimulation site (V1-R) ensures the relative target specificity of any behavioral effect observed following tDCS over the PPC after a reminder (Parkin et al., 2015).

For the PPC-NR group, the same experiment of Day 1 administered the experimental procedure in a different spatial context (i.e. different experimental room), a behavioral manipulation previously successfully done in human reconsolidation studies (Hupbach et al., 2008; Sandrini et al., 2013). The experimenter only applied tDCS without presenting the blue bag and without asking what happened on Day 1. Stimulation of the PPC without the reminder is a control condition to ensure that any behavioural effect observed following tDCS over the PPC after a reminder (PPC-R) is specific to memory reactivation (Sandrini et al., 2013).

In all groups, the electrodes were removed after 20 minutes and the participants were asked to complete a questionnaire of sensations related to transcranial electrical stimulation (Antal et al., 2017).

We choose these active control conditions instead of the frequently used sham stimulation procedure in order to examine two contrasts: whether the behavioural effect of tDCS applied over the left PFC after memory reactivation is topographically specific (vs. stimulation over V1 after memory reactivation), and whether the behavioural effect of tDCS applied over the left PPC is reactivation specific (vs. stimulation over the left PPC without memory reactivation).

Since non-invasive stimulation of non-motor areas, such as PPC, does not induce immediate, observable neurophysiological effects, the inclusion of a robust positive control is challenging. However, the selective influence of tDCS over the PPC on episodic memory has been demonstrated (Jacobson et al., 2012; Jones, Gözenman, & Berryhill, 2014; Pergolizzi & Chua, 2016; Pisoni et al., 2015).

On Day 3 (48 hours after the learning session), an experimenter not involved during the learning phase (Day 1) and tDCS session (Day 2) asked the participants to recall as many words as possible from the list learned on Day 1, and the experimenter noted the words recalled, including words that were not on the list (intrusion errors).

When participants indicated that they cannot remember any more words, the experimenter engaged the participants in a conversation about an unrelated topic for about 30 seconds. The experimenter then repeated the recall test by asking the participants to recall the words again. As in previous reconsolidation studies (Hupbach, Gomez, Hardt, & Nadel, 2007; Hupbach et al., 2008; Sandrini et al., 2013; Sandrini et al., 2014) this procedure will be repeated for four consecutive recall trials to test reliability of recall.

2.5 Proposed statistical analysis

A person, who was not aware to which experimental group the data belong, performed the statistical analyses using IBM SPSS software version 24 and the R statistical computing environment (R Core Team, 2019) for Bayesian analysis.[1]

Sensations related to tDCS and memory strategies were compared between the three experimental groups using the Kruskal–Wallis test, with follow-up Mann-Whitney U tests where appropriate.

Learning performance on Day 1: To compare the learning rate of the three experimental groups, we recorded how many learning trials (1–4) were necessary for participants to recall at least 17 words (85%). As in previous reconsolidation studies (Sandrini et al., 2013; Hupbach et al., 2007; Hupbach et al., 2008), participants who recall <17 words during the fourth learning trial will be given a score of 5. In a previous reconsolidation study in young adults, participants needed on average 3.4 learning trials to reach this criterion (Sandrini et al., 2013). To test for equality of learning rates between groups, Bayesian hypothesis testing was used to provide positive evidence in favour of null hypothesis over alternative hypothesis (Dienes et al., 2014). We estimated Day 1 learning rates of the three experimental groups in a Bayesian Markov Chain Monte Carlo ordered probit regression model as described in Kruschke (2014) with learning rates as ordinal dependent variable, and experimental group as independent variable. This analysis was run using the Zelig R package (Choirat, Honaker, Imai, King, & Lau, 2018). 100000 iterations were used for

[1] The software package used for running Bayesian regression deviates from the original protocol in Stage 1. The change to R was motivated by the aim to allow the reproducibility of this analysis in an open-access, free statistical package.

estimation, with a burn-in period of 5000. We evaluated differences using 95% Highest Probability Density (HPD) credible intervals of between-group coefficients using a normal prior (mu=0, SD=100), calculated using the HDInterval R package (Meredith & Kruschke, 2018).[2]

Memory performance on Day 3:

Only the words correctly recalled across the 4 recall trials were included in the analysis. Intrusion errors were not computed in the total score of each participant. In young adults, there are often too few intrusions errors available for analysis (Wingfield, Lindfield, & Kahana, 1998). In a previous reconsolidation study in young adults, the mean number of intrusion errors was on average 0.43 (Sandrini et al., 2013).

The mean percentage of words correctly recalled were compared between the three experimental groups using one-way analysis of variance (ANOVA) for independent samples. If statistically significant, a priori multiple comparisons were planned (PPC-R vs PPC-NR; PPC-R vs V1-R; PPC-NR vs V1-R) using independent samples t-test (two-tailed), and the p-value was Bonferroni-corrected for the number of comparisons (p= 0.05/3 = 0.0167).

If the groups differed on reported sensations or memory strategies, one-way analysis of covariance (ANCOVA) was planned to be performed.

[2] Details of the R code and analysis are available online at the URL: https://figshare.com/projects/Effects_of_tDCS_over_posterior_parietal_cortex_on_episodic_memory_reconsolidation/64793.

In a previous reconsolidation study in young adults, participants correctly recalled 73% of words in the PFC-R, 56.3% in the PFC-NR, and 56.6% in the vertex-R (Sandrini et al., 2013).

Results

Eighty-one participants were included in the analysis. No participants were excluded from the analysis because immediate recall performance after the last learning trial (Day 1) was less than 2.5 standard deviation from the mean of the group. The mean score for the Edinburgh Handedness Inventory was 95.5.

Anonymized raw data with guidance notes are available on Fig share: (https://figshare.com/projects/Effects_of_tDCS_over_posterior_parietal_cortex_on_episodic_memory_reconsolidation/64793).

No significant differences were found between groups in memory strategies (H_2=2.64 p=.27) and sensations induced by tDCS (H_2=2.6 p=.27) (see Table 1). Overall, the participants learned the words in 3.9 trials.

To test the equality of learning between groups, we conducted Bayesian ordered probit regression. The analysis script (including simulation diagnostics) are available as supplementary material at the URL above. Mean learning rate estimate was 2.697. Thresholds for ordinal variable 'learning rates' values 1 to 5 were estimated as (0; 1.184; 2.187; 2.619). 95% HPD credible intervals for control versus experimental group differences were [-1.127, 0.062; PPC-NR versus PPC-R] and [-0.777, 0.437; V1-R versus PPC-R]. Since a one learning trial mean difference between groups were plausible parameter values based on these intervals, an ANCOVA model was chosen to account for

the potential effect of Day 1 learning performance affecting long-term recall (Day 3), as per a priori data analysis plan.

INSERT TABLE 1 HERE

One-way ANCOVA on memory performance on Day 3 shows that the main variable "group" was not significant $F(2,77)=.451$, $\eta_p^2=.012$, $p=.639$, indicating no differences between groups in the mean recall (see Table 2). The covariate (max. number of words recalled in the learning session) had a significant effect on Day 3 memory performance, $F(1,77)=35.135$, $\eta_p^2=.313$, $p<.001$.

We also conducted analysis on the intrusion errors. One-way ANOVA shows no differences between groups $F(2,78)=0.5$, $\eta_p^2=.001$, $p=.95$ (see Table 2).

INSERT TABLE 2 HERE

Discussion

In the present study, the effects of tDCS over the left ventral PPC through reconsolidation were studied. The results did not support a positive effect of tDCS over the left PPC after episodic memory reactivation according to the behavioural outcome measure, mean word recall on day 3.

The lack of tDCS-induced memory enhancement may be rooted in multiple factors. There was no evidence for group differences in the use of memory strategies or sensations induced by tDCS, and potential difference in learning rate were accounted for in our analyses. Thus, the non-significant effects of tDCS over the left ventral PPC cannot be

explained by discomfort or memory strategies. The three groups performed compatibly on the free recall test. Based on the premise that no beneficial effect of tDCS occurred, one potential interpretation would suggest that left ventral PPC does not carry neural underpinnings that are crucial to the reconsolidation process.

In concordance with the literature, most theorists place greater casual emphasis on MTL and PFC in episodic memory (Dudai, 2012; Sandrini et al., 2013; Dickerson & Eichenbaum, 2010; Bilek et al., 2013; Eichenbaum, 2017; Nadel et al., 2000). The standard model of memory consolidation argues that the initial stages of encoding, storage and retrieval are heavily contingent on the hippocampus and increasingly the neocortex (Dudai, 2012; Nadel et al., 2000). The speculative role of PPC in memory is based on relatively new research and remains controversial (Berryhill, 2012; Cabeza et al., 2012; Rugg & King, 2018; Rugg & Vilberg, 2013; Sestieri et al., 2017; Uncapher & Wagner, 2009). The region is mainly involved in attentional processes, and it may therefore be that the mnemonic contribution of the left ventral PPC is minimal (Sestieri et al., 2017). In line with previous research, the marginal role of the left ventral PPC in memory may not be enough to alter neuronal functioning in dominant mnemonic brain regions. It is important to note, however, that the evidence for the standard model of memory consolidation does not provide a full understanding of the reconsolidation process (Nadel et al., 2000). Thus, the notion does not offer an unchallenged alternative explanation of the current results.

The study presents a focused investigation on the role of PPC in reconsolidation. However, potential exogenous influences on the current negative findings must be considered. It is possible that the chosen tDCS electrode montage and stimulation parameters may not be optimal for the current research objective. tDCS montages other than the CP5-Cz setup

used in the current study may be more efficient in targeting the left ventral PPC. Future studies could make use of electric current modelling software (e.g. HD-Target, Soterix Medical) to determine the optimal electrode configuration for the chosen brain target. Regarding the stimulation parameters, if the left ventral PPC lends support to reconsolidation in a large-scale network-manner (Chun & Turk-Browne, 2007; Craik, 2001; Uncapher & Wagner, 2009), it may be that an electrical current of 1.5 mA is insufficient to probe altered network connectivity via an area that serves as a secondary contributor to MTL and PFC. Subsequently, reaching a certain current threshold may be required to yield beneficial effects. Based on intra- and extracellular density recordings of tDCS using animal and cadaver models, Voroslakos et al. (2018) suggest that potentially only 25% of the applied electrical current applied penetrates brain tissue, and thus, typically used current densities may not be sufficient to achieve sufficient neural response. At the same time, there is some evidence suggesting that performance may improve in a current-dependent manner and that 2mA but not 1mA produced behavioural improvements (Teo, Hoy, Daskalakis, & Fitzgerald, 2011; Boggio et al., 2006). Different current strengths have also been shown to serve different effects on the underlying cortical region as some current strengths may depolarise inhibitory rather than excitatory interneurons, affecting the interlinked behaviour accordingly (Priori et al., 1998; Arul-Anandam & Loo, 2009).

Another potential alternative explanation of lack of enhancement found in our study is that a large body of work implicates dorsal PPC rather than ventral PPC in successful memory performance (Uncapher & Wagner, 2009). In terms of localisation, it may therefore be that stimulating the bottom-up, stimulus-driven ventral PPC may not serve any beneficial outcomes toward performance in a paradigm that arguably requires top-down control

(Corbetta et al., 2008). The current research cannot rule out the probability that dorsal PPC is involved in successful memory performance, with potentially dissociable contributions of ventral and dorsal PPC. It may therefore be hypothesised that reconsolidation is not supported by bottom-up driven, ventral PPC regions and that ventral and dorsal PPC have separable neural and behavioural mechanisms. This model does not rule out the supposition that superior parietal regions aid reconsolidation. In line with this proposal, beneficial effects of increased dorsal PPC activity have been documented in behavioural measures of memory performance (Uncapher & Wagner, 2009). The current study acknowledges that there is a case for both rejecting the role of PPC in reconsolidation, and for accepting the dissociable roles of ventral and dorsal PPC. Further examination is therefore required to determine whether PPC carries mnemonic properties.

The present study implicates that there may not be a clinical advantage of stimulating the left ventral PPC (CP5). In comparison to established regions such as left PFC, on which NIBS produces long-lasting beneficial effects on reconsolidation (Manenti et al., 2017, 2018; Sandrini et al., 2013), no effect occurred in a healthy population. The study therefore suggests stimulation of other regions in clinical populations with memory disorders, e.g. PFC and MTL may be more advantageous as potential future clinical intervention targets. Practically, the results of the current study contribute to the localisation of function. As demonstrated, memory modification will not occur without precise stimulation, and moving towards accurate and validated stimulation parameters for clinical implications is necessary.

The current findings may offer some guidance to future research. Considering the elusive nature of positive tDCS results, further research should make strides toward assisting the

delineation of accurate stimulation parameters and theoretical interpretations. Further studies should first aim to replicate the current paradigm with adjusted stimulation parameters. Most importantly, a slight increase in the applied current strength could be made (2 mA). This will contribute toward establishing whether the lack of enhancement found in the current study could be due to the targeted area of PPC not playing a key role in reconsolidation.

Future research should further expand on the current findings by updating the electrode localisation. By targeting P3 according to the 10–20 EEG international electrode scalp positioning system (Jasper, 1958), dorsal PPC could be targeted instead of ventral PPC. The use of high-definition tDCS (HD-tDCS) or Transcranial Magnetic Stimulation (TMS), techniques that produces more focal neuronal modulation (Sandrini et al., 2011; Villamar et al., 2013), may be more optimal. Furthermore, combining tDCS with task-based or resting state fMRI would enable more accurate localisation of targeted regions (Shafi et al., 2012; Venkatakrishnan and Sandrini, 2012; Wang et al., 2014).

Conclusions

The current research adopted a pre-registration approach to disentangling neurophysiological processes associated with episodic memory reconsolidation. The study moved away from the conventional targeting of the PFC-MTL network and explored the role of left ventral PPC in reconsolidation of episodic memory by using tDCS. The results did not support the hypothesis, finding no evidence that stimulation of CP5 after reconsolidation produces beneficial outcomes on episodic memory. Although this could indicate that PPC is not crucial to reconsolidation, several alternative interpretations remain

plausible and require further examination. Improving stimulation parameters and targeting precision could be crucial components of future progress. Literature in support of the mnemonic role of PPC is abundant, and future tDCS research could explore contributions of this brain region to memory reconsolidation with increased the current strength and revised (P3 rather than CP5) stimulation montage.

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Figure legends

Figure 1. Current flow model of tDCS montage with the anode (5x5 cm^2) over CP5 and cathode (7x8 cm^2) over Cz represented in lateral, sagittal, and transverse views from the Soterix HD Targets software (Soterix Medical). Arrows represent direction of current flow.

Figure 2. Participants learned 20 words on Day 1 (at least 17/20). On Day 2 (24h later), existing memories were reactivated by a contextual reminder (same exp. room of Day 1), and after 10 min tDCS was applied over the PPC or V1 (PPC-R and V1-R respectively). In a third group of participants, tDCS was applied over the PPC without memory reactivation (different exp. room) (PPC-NR). Memory retrieval (free recall) was tested on Day 3 (48h after the learning session).

Table 1. Mean and standard deviation (in brackets) for memory strategies score, tDCS-induced sensations and learning rate.

Group	Memory strategies	tDCS sensations	Learning rate
PPC-R	17.74 (5.65)	3.19 (2.89)	4.15 (0.9)
PPC-NR	15.74 (4.53)	3.93 (2.3)	3.63 (1.15)
V1-R	16.48 (6.89)	3.30 (2.01)	4 (1.24)

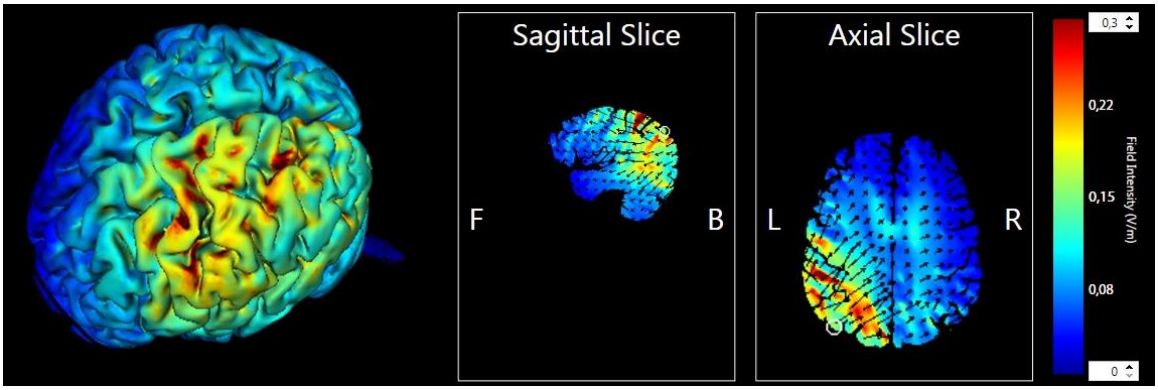
Table 2. Memory performance on Day 3. Mean and standard deviation (in brackets) of words recalled and intrusion errors across 4 trials.

Group	Mean Recall Day 3	Intrusion Errors Day 3
PPC-R	10.43 (2.43)	0.81 (1.39)
PPC-NR	11.27 (3.00)	0.70 (1.77)
V1-R	11.18 (3.44)	0.70 (1.2)

Appendix A
List of words

UNIFORM
BOTTLE
ENGINE
ORCHESTRA
VALLEY
DETECTIVE
COUNTRY
LETTER
CLOTHES
SHOULDER
TELEPHONE
FOREST
BUILDING
LIBRARY
ISLAND
COLUMN
PAINTING
PLATFORM
CATTLE
NEWSPAPER

947 Figure 1



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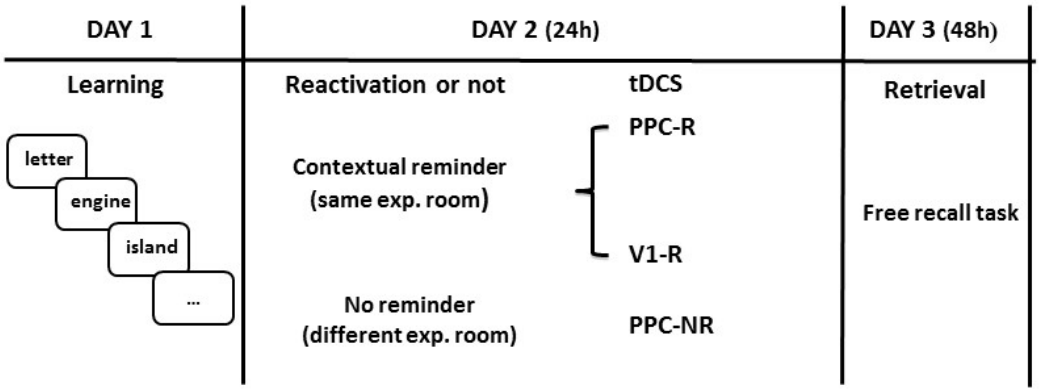
951 Figure 2



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