Brain Stimulation 14 (2021) 1005–1014

Contents lists available at ScienceDirect

Brain Stimulation

journal homepage: http://www.journals.elsevier.com/brain-stimulation

Polarity-specific high-definition transcranial direct current stimulation of the anterior and posterior default mode network improves remote memory retrieval

Yuefeng Huang [a], Anusha Mohan [b, c, d], S. Lauren McLeod [a], Alison M. Luckey [b, c, d], John Hart Jr. [a], Sven Vanneste [a, b, c, d, *]

[a] School of Behavioral and Brain Sciences, The University of Texas at Dallas, Richardson, TX, USA
[b] Global Brain Health Institute, Trinity College Dublin, Dublin, Ireland
[c] Trinity College Institute for Neuroscience, Trinity College Dublin, Dublin, Ireland
[d] Lab for Clinical & Integrative Neuroscience, School of Psychology, Trinity College Dublin, Dublin, Ireland

ARTICLE INFO

Article history:
Received 1 December 2020
Received in revised form
10 June 2021
Accepted 15 June 2021
Available online 23 June 2021

Keywords:
Medial prefrontal cortex
Posterior cingulate cortex
Anodal stimulation
Cathodal stimulation

ABSTRACT

Background: Previous studies show that activity in the posterior default mode network (pDMN), including the posterior cingulate cortex and the precuneus, is correlated with the success of long-term episodic memory retrieval. However, the role of the anterior DMN (aDMN) including the medial prefrontal cortex is still unclear. Some studies show that activating the medial prefrontal cortex improves memory retrieval while other studies show deactivation of the medial prefrontal cortex in successful retrieval of episodic memories, suggesting a possible functional dissociation between the aDMN and pDMN.

Objective: In the current study, we aim to causally explore this probable dissociation using high-definition transcranial direct current stimulation (HD-tDCS).

Methods: We perform a randomised double-blinded two-visit placebo-controlled study with 84 healthy young adults. During Visit 1 they learn 75 Swahili-English word-associations. Seven days later, they randomly receive either anodal, cathodal or sham HD-tDCS targeting the pDMN or aDMN while they recall what they have previously learned.

Results: We demonstrate that anodal stimulation of the pDMN and cathodal stimulation of the aDMN, equally improve the percentage of Swahili-English word-associations recalled 7 days after learning.

Conclusions: Modulating the activity in the aDMN and pDMN causally affect memory retrieval performance. HD-tDCS of the aDMN and pDMN shows that anodal stimulation of the pDMN and cathodal stimulation of the aDMN increases memory retrieval performance one week after the learning phase. Given consistent evidence, it is highly likely that we are increasing the activity in the pDMN with anodal pDMN stimulation. However, it is not clear if cathodal HD-tDCS targetting aDMN works via decoupling from the pDMN or via indirectly disinhibit pDMN.

Introduction

Recalling memories is a basic survival instinct. At a molecular level, memories are stored in cells called engrams and retrieved when the synaptic strength of connections between them is increased [1,2]. At a systems level, neuroimaging studies demonstrate a relationship between the connectivity of the medial temporal lobe (MTL) and default mode network (DMN), particularly the posterior part of the DMN, and successful retrieval of long-term episodic memories [3,4]. The DMN is often considered as a functionally homogenous brain network because of the high reproducibility of its role across different methods and experimental conditions [5]. It consists of two main parts – the anterior section and the posterior sections [6,7] that form its core. The anterior DMN

* Corresponding author. Lab for Clinical & Integrative Neuroscience, School of Psychology, Global Brain Health Institute, Institute of Neuroscience, Trinity College Dublin, College Green 2, Dublin, Ireland.
E-mail address: sven.vanneste@tcd.ie (S. Vanneste).
URL: http://www.lab-clint.org

https://doi.org/10.1016/j.brs.2021.06.007

(aDMN) includes prefrontal areas such as the medial prefrontal cortex (mPFC), whereas the posterior DMN (pDMN) includes the posterior cingulate cortex (PCC) and precuneus [6,8]. The current study explores whether polarity-specific neuromodulation of the aDMN and pDMN both result in improved performance during episodic memory retrieval in young, non-cognitively impaired adults.

Functional magnetic resonance imaging (fMRI) indicates that successful memory retrieval is associated with increased activity in the pDMN regardless of the type of stimulus modality, and memory test [9–13]. Unlike research surrounding increased activity in the pDMN and successful memory retrieval, the aDMN's evidence is still inconsistent. Reactivating engram cells in the mPFC could lead mice to re-experience fear memory formed previously even in the absence of an actual context [14]. In humans, activation of the mPFC is consistently reported during recall of auto-biographical information [15–17]. However, a study also reported a functional dissociation between the aDMN and pDMN during episodic memory retrieval [18]. Specifically, the pDMN was highly activated and the aDMN was strongly deactivated [18]. Other research corroborated this evidence by showing that decoupling of the mPFC from the rest of the DMN benefits schema memory [19]. These studies suggest that the aDMN and pDMN may have diametrically opposing functionalities during episodic memory retrieval.

In the current study, we aim to disentangle the role of the pDMN and aDMN in episodic memory retrieval using a neuromodulation technique called high-definition transcranial direct current stimulation (HD-tDCS) [20–22]. Compared to conventional tDCS, which uses large electrode pads, HD-tDCS uses an array of small, circular electrodes. This makes it possible to stimulate brain regions with increased spatial accuracy [23]. tDCS has two types of stimulation – anodal and cathodal stimulation. Anodal stimulation is where the positive electrode is placed over the targeted region and current flows away from it towards the return electrode placed away from the targeted region; vise-versa happens in cathodal stimulation [23]. The general effect of tDCS is assumed to be anodal excitation and cathodal inhibition [24–26]. However, other research indicates that this polarity-specific effects of tDCS is specific to the motor cortex [27–30], but this effect of tDCS for non-motor regions might be different [31]. That is, research revealed that both anodal and cathodal tDCS could increase synaptic strength of connections between different brain regions [32,33].

Based on the above literature, a potential functional dissociation between the aDMN and pDMN during episodic memory retrieval and the fact that tDCS increases synaptic strength between different brain regions, we hypothesize that anodal HD-tDCS targeting the pDMN can improve memory retrieval. Yet, HD-tDCS targeting the aDMN can improve memory retrieval, but it is not clear if this can be achieved by anodal or cathodal stimulaiton. Through this study, we will be able to further our understanding of the potential relationship between the DMN and the memory retrieval process. It can provide valuable information for future therapeutic approaches that could utilize brain stimulation to help memory-related disorders such as Alzheimer's disease (AD) and mild cognitive impairment (MCI) that involve malfunctions of either the aDMN or pDMN.

Methods

Design

This study is a double-blinded, two-visit, placebo-controlled, randomized, parallel-group study. The study employed a mixed factorial design with time (Visit 1 vs. Visit 2) as the within-subjects factor and stimulation condition (anodal vs. cathodal vs. sham stimulation) and stimulation location (aDMN vs pDMN) as the between-subjects factors which serve as independent variables, whereas the number of recalled English–Swahili word-pairs is the dependent variable. The study was approved by the University of Texas at Dallas (UTD) Institutional Review Board (IRB), and all participants signed the informed consent before starting the study.

Sample size

The sample was estimated based our previous research using the word asscoaition task [34] (see experiment 5). It is important to note that in the previous study the stimulation was applied during the first visit using an occipital target. However, as the primary outcome, the word asscoaition task during Visit 2, was similar as in previous study we used this to estimated the sample size in the present study. We calculated our sample by assuming an α level of 0.05 (two-sided), power of 90%, and an effect size of $\eta^2 = 0.50$ on word association test during Visit 2. This resulted in a sample size of 72. We included extra participants to anticipate a drop-out between Visit 1 and Visit 2.

Participants

We recruited a total of 84 participants from the UTD main campus. Fourty participants (male = 9, mean age = 19 years, *Sd* = 1.5 years) were included in the aDMN group (13 anodal, 14 cathodal, and 13 sham stimulation). For pDMN, a total of 44 participants (male = 11, mean age = 19 years, *Sd* = 1.2 years) were included (16 anodal, 11 cathodal, and 17 sham stimulation). The study inclusion criteria were: (i) age 18–35 years; (ii) not currently using any medication; (iii) native English speakers, i.e., born and raised in the United States or have been speaking, living, or going to school in the United States since six years of age or younger; and (iv) capable of understanding and signing the informed consent form. The study exclusion criteria were: (i) acquainted with the Swahili/Arabic language or Swahili culture; (ii) severe disease; (iii) mental illness; (iv) cardiac history; (v) history of severe head injuries; (vi) history of epileptic insults; (vii) implanted devices such as a pacemaker or neurostimulator; and (viii) pregnancy. To check these criteria, all participants were phone-screened prior to scheduling appointments for study sessions. In addition, during the visit and after consenting we tested and excluded participants who scored (i) > 13 on Beck Depression Inventory-II Questionnaire (BDI-II) (ii) 2 or above on the suicide question including in the BDI-II and (iii) < 30 on the Mini-Mental State Examination (MMSE).

Testing material

For the memory task, we used a well established English–Swahili word-pairs test, based on an associative memory test paradigm adapted from previous studies [35,36], the merits of which include – (1) reduced exposure to Swahili vocabulary among English-speaking participants; (2) reduced likelihood of participants learning Swahili in a school setting, since it's not related to the Romance languages; (3) Swahili using the Standard English alphabet without modifications of any letters and (4) optimal recall performance of ~20% correct, which is well above the floor but allows ample room for assessment of differences in multi-trial learning [35].This task was conducted in both Visit 1 and Visit 2 sessions. During Visit 1, participants repeatedly studied and were tested on the English-Swahili word-pairs in an attempt to correctly learn all 75 word-pairs by the end of the visit. On Visit 2, seven days later, they were asked to recall all 75 word-pairs from Visit 1. While performing this recall test during Visit 2, each participant randomly

received either anodal, cathodal, or sham HD-tDCS targeting the aDMN or pDMN.

Word association task

1. Visit 1

During Visit 1, participants first went through the informed consent. After all pre-assessments, instructions were provided to the participants on the English–Swahili word-pairs test. In Visit 1, the test contained four blocks using a SDT_N paradigm (S, study phase; D, distraction phase; T_N, test phase with non-recalled word pairs) [36]. Each block included a study phase, a distraction phase, and a test phase. Participants studied all 75 word-pairs in every block but, after a Swahili word is successfully recalled once during a test phase, that word-pair would be dropped from the test phases of subsequent blocks. Previous research demonstrated the critical role of retrieval practice in the consolidated learning of a foreign language [36]. Therefore, applying the SDT_N condition ensures that all participants were well exposed to the study material while avoiding a ceiling effect on the number of Swahili words learned during Visit 1. This creates enough room to assess the memory performance between stimulation conditions and targeted brain regions. During the study phase each word-pair was presented for 5 s. During the test phase each Swahili word was presented for 8 s for the participant to provide the correct English translation. After Visit 1 was completed, participants were asked to refrain from studying the word pairs learned throughout the week.

2. Visit 2

Seven days later, participants returned for Visit 2. To rule out the possible effects of HD-tDCS on mood that might confound its memory effect on the retrieval test, the experimenter asked participants to fill out the Profile of Mood States (POMS) questionnaire before and after HD-tDCS. Since this is a double-blinded study, a second experimenter conducted the word-pairs retrieval test as well as the HD-tDCS procedure. The experimenter randomly selected a ticket out of a raffle-like box to assign each participant to either anodal, cathodal, or sham stimulation targeting either the aDMN or pDMN. Following the word-pairs test paired with HD-tDCS, participants were then asked to complete a tDCS Interference Questionnaire and Exit Questionnaire [37].

Simulation procedure

Before the actual stimulation procedure, a fully automated Realistic Volumetric-Approach to Simulate Transcranial (ROAST https://www.parralab.org/resources.html) [38] electric simulation pipeline was used to find the ideal electrode placement for stimulation of aDMN and pDMN. ROAST is a Matlab based toolbox that combines the segmentation algorithm of SPM8 and automatic electrode placement, the finite element mesher iso2mesh and the solver getDP [38]. The electrode placement was setup according to the 10/20 international system for EEG electrode placement, using Fpz as the stimulation electrode and Fz, Fp1, and Fp2 as returning electrodes for aDMN stimulation (Fig. 1a), and using Pz as the stimulation electrode and Oz, PO7, and PO8 as returning electrodes for pDMN stimulation (Fig. 1b). The electric fields and voltage maps as well as the electrode montages for both aDMN and pDMN stimulation are displayed in Fig. 1 (we used anodal stimulation for both aDMN and pDMN as examples here). The electric field describes the direction of the direct current and areas it passes through. The voltage map describes the polarity of the stimulation. The electrode montage describes the location of the electrodes of the stimulation on a human head model. Both setups called for a constant current of 1.0 mA. The model corroborated that our HD-tDCS montages produced maximum current flow to the aMDN, including the ventral mPFC (vmPFC) and dorsal mPFC (dmPFC), and to the pDMN consisting of the PCC and precuneus. The simulation model was based on the MNI-152 standard head [39].

HD-tDCS procedure

Direct current was transmitted through circular Ag/AgCl electrodes (1-cm radius) attached to a neoprene head cap using a conductive gel and was delivered by a battery-driven, wireless multichannel transcranial current stimulator (Starstim tCS®, http://www.neuroelectrics.com). The stimulation montages were based on the simulation procedure as described above. We applied HD-tDCS only during Visit 2.

The central electrode was set up as the anode or the cathode, respectively, in the anodal and cathodal stimulation conditions. See Fig. 1 for montages. In both stimulation conditions, after a 60 s ramp-up period (gradual increase), we added 30 s for participants to habituate to the stimulation before the memory retrieval task started. The retrieval test phase would then begin, lasting 10 min (= 8 s per words x 75 words). After the retrieval test phase, stimulation immediately ramps down (gradually decrease) for 30 s. The total actual stimulation time is 10 min 30 s. In the sham stimulation group, the simulation immediately ramps down for 30 s during the habituation period after the initial 60 s ramp up. The rationale behind this sham procedure is to mimic the transient haptic sensation at the beginning of active HD-tDCS. The sham session lasts as long as the active HD-tDCS session to appropriately blind the procedure. For all three stimulation conditions, the stimulation intensity was set at 1.0 mA.

Statistical analysis

For Visit 1, the percentage of words (recalled/total words (i.e. 75)) cumulatively learned in each study block was compared between the different areas and stimulation groups using a repeated measures ANOVA including area (aDMN vs. pDMN) x condition (anodal vs. cathodal vs. sham) as between-subjects variables and study blocks (block, 1, block 2, block 3 and block 4) as within-subjects variable. We tested for sphericity using the Mauchly's test of sphericity, it the assumption was violated we applied a GreenGeisser correction.

For Visit 2, seven days after learning the word associations, we analyze the data in two different ways. In the first method, the percentage of how many words presented, we divided the correctly retrieved words during Visit 2 by the entire list of words (i.e. 75 words). In the second method, the percentage of how many words learned during Visit 1, we divided the correctly retrieved words during Visit 2 by the number of words participants successfully remembered during Visit 1. In both analyses we used an ANOVA with the percentage of how many words presented (i.e. 75 words) and how many words learned during Visit 1, respectively as dependent variable and area (aDMN vs. pDMN) and condition (anodal vs. cathodal vs. sham) as the independent between-subjects variables. To compare the different conditions or area we used a simple contrast analysis. A Bonferoni correction was applied to correct for multiple comparisons.

We compared Visit 1 with Visit 2 (raw scores) including the condition and area as between-subjects variables using a repeated measures ANOVA. We tested for sphericity using the Mauchly's test of sphericity, it the assumption was violated we applied a Green-Geisser correction.

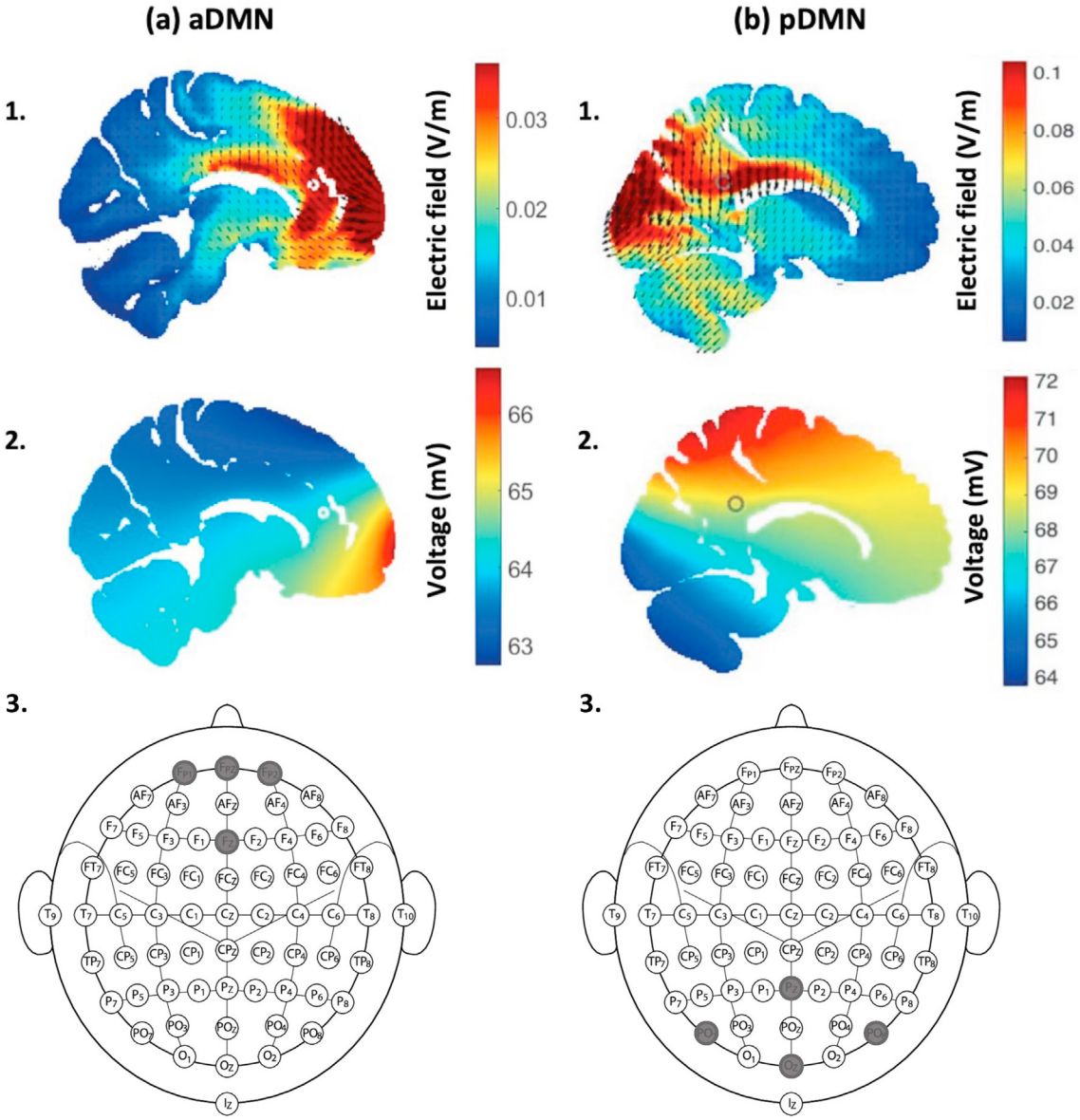

Fig. 1. (a) Simulation model from ROAST targeting aDMN using Fpz as the stimulation electrode and Fz, Fp1, and Fp2 as returning electrodes for stimulation intensity as 1.0 mA. The upper row (**1**) demonstrated the electric field, the middle row (**2**) demonstrated the voltage map and the lower row (**3**) demonstrated the electrodes montage (re-drawn from Ref. [67]). (b) Simulation model from ROAST targeting pDMN using Pz as the stimulation electrode and Oz, PO7, and PO8 as returning electrodes for stimulation intensity as 1.0 mA. The upper row (**1**) demonstrated the electric field, the middle row (**2**) demonstrated the voltage map and the lower row (**3**) demonstrated the electrodes montage (re-drawn from Ref. [67]).

For the POMS questionnaire we used repeated measures ANOVA to analyze the stimulation effect on mood with POMS total score (before vs. after stimulaiton) as within-subjects variable, and area (aDMN vs. pDMN) and condition (anodal vs. cathodal vs. sham) as between-subjects variables.

Before concluding the experiment, participants were asked to fill out a questionnaire to assess their experience of possible side effects (e.g., headache, neck pain, and scalp pain) related to the stimulation on a 4-point scale (1 = absent, 2 = mild, 3 = moderate, and 4 = severe). We performed a MANOVA to assess the differences between scores on side effects between anodal, cathodal, and sham stimulation conditions for the two areas (aDMN vs. pDMN).

In addition, we asked participants if they were assigned to the active (anodal or cathodal) or sham group. We performed a chi-square analysis to assess if participants in all three stimulation conditions were well-blinded during the stimulation session and compared participants' perception of the stimulation with the actual stimulation.

Results

Word association task

For Visit 1, a repeated measures ANOVA (using a GreenGeisser correction) including area (aDMN vs. pDMN) x condition (anodal vs. cathodal vs. sham) x study blocks (block, 1, block 2, block 3 and block 4) revealed no significant effect for area ($F(1,78) = 1.02$, $p = .32$), condition ($F(2,78) = 2.44$ $p = .094$), area x condition (F

(2,78) = 0.96, $p = .39$), area x study block (F (3,76) = 0.71, $p = .55$), condition x study blocks (F (6,154) = 1.22, $p = .30$), or area x condition x study blocks (F (6,154) = 0.87, $p = .52$), indicating that there is no difference between the area and conditions stimulated over the different study blocks. As expected we found a significant effect for block (F (3,76) = 1349.76, $p < .001$) indicating that participants learned more words after every block. Pairwise comparison using a Bonferroni correction of multiple comparison revealed that participants learned more words after block 4 ($M = 85.48\%$, $Sd = 16.02$, F (1,78) = 2508.16, p < .001) in comparison to the three other blocks. For block 3 ($M = 71.41\%$, $Sd = 19.21$, F (1,78) = 1418.47, $p < .001$) participants learned more words in comparison to the two previous blocks. In block 2 ($M = 45.79\%$, $Sd = 18.66$, F (1,78) = 580.22, $p < .001$) participants learned more words in comparison to block 1 ($M = 14.49\%$, $Sd = 9.25$). See Fig. 2a for overview.

For Visit 2, seven days after learning the word associations, we analyzed the data in two different ways, namely based on how many words presented (i.e. 75 words) and based on how many words learned during Visit 1. Based on how many words presented, an ANOVA revealed a significant main effect for condition (F (2,78) = 3.33 $p = .04$), but no mian effect for area (F (2,78) = 2.55, $p = .11$). For condition, a pariwise comparison using a Bonferroni correction of multiple comparison revealed that sham stimulation ($M = 31.55\%$, $Sd = 19.05$) was significantly different from cathodal ($M = 41.39\%$, $Sd = 15.52$, F (1,78) = 3.82 p = .047) and anodal ($M = 42.16\%$, $Sd = 15.14$, F (1,78) = 5.84, $p = .018$) stimulation. No significant effect was obtained between cathodal and anodal stimulation. Yet, this main effect for condition interacts with area, showing an interaction effect between area x condition (F (2,78) = 5.17, $p = .008$). For pDMN, a simple contrast analysis revealed that participants assigned to the anodal conditions ($M = 45.25\%$, $Sd = 14.92$) recalled significantly more words in comparison to the cathodal ($M = 29.70\%$, $Sd = 12.37$, F (2,78) = 6.26, $p = .014$) and sham ($M = 30.35\%$, $Sd = 22.54$; F (2,78) = 3.33, $p = .041$) groups. These effects remained after correction for multiple comparison using a Holm-Boneferonni correction. For aDMN, a simple contrast analysis revealed that participants assigned to the cathodal conditions ($M = 50.57\%$, $Sd = 11.00$) recalled significantly more words in comparison to the anodal ($M = 38.36\%$, $Sd = 15.10$, $F = 3.99$, $p = .049$) and sham ($M = 33.13\%$, $Sd = 13.97$; F (2,78) = 8.14, $p = .006$) groups. These effects remained after correction for multiple comparison using a Holm-Boneferonni correction. No significant effect was obtained when comparing the cathodal condition for pDMN group with anodal condition for aDMN group (F (2,78) = 1.76, $p = .19$). See Fig. 2b for overview.

Based on how many words learned during Visit 1, an ANOVA demonstrated a significant main effect for area (F (1,78) = 4.85 $p = .031$), but no main effect for condition (F (2,78) = 1.64 $p = .20$). This effect for area revealed that participants assigned to the aDMN group ($M = 46.87\%$, $Sd = 12.92$) recalled more words in comparison to the pDMN group ($M = 39.51\%$, $Sd = 18.62$). This main effect, however, interacts with condition, showing an interaction effect between area x condition (F (2,78) = 5.62, $p = .005$). For pDMN, a simple contrast analysis revealed that participants assigned to the anodal conditions ($M = 48.47\%$, $Sd = 14.38$) recalled significantly more words in comparison to the cathodal ($M = 33.99\%$, $Sd = 13.06$, F (2,78) = 5.96, $p = .017$) and sham ($M = 36.07\%$, $Sd = 22.76$; F (2,78) = 5.52, $p = .021$) groups. These effects remained after correction for multiple comparison using a Holm-Boneferonni correction. For aDMN, a simple contrast analysis revealed that participants assigned to the cathodal condition ($M = 56.02\%$, $Sd = 8.48$) recalled significantly more words in comparison to the anodal ($M = 42.64\%$, $Sd = 14.21$, $F = 5.26$, $p = .024$) and sham ($M = 41.94\%$, $Sd = 12.92$; F (2,78) = 5.81, $p = .018$) groups. These effects remained after correction for multiple comparison using a Holm-Boneferonni correction. No significant effect was obtained when comparing the cathodal condition for pDMN group with anodal condition for aDMN group (F (2,78) = 1.94, $p = .17$). See Fig. 2c for overview.

As a final analysis, we compared Visit 1 with Visit 2 (raw scores) including the condition and area as between-subjects variables using a repeated measures ANOVA (using a GreenGeisser correction). Our data revealed a significant effect for visit (F (1,78) = 962.20, $p < .001$), and condition (F (2,78) = 5.78, $p = .005$), but no significant effect for the area stimulated was obtained (F (1,78) = 0.46, $p = .50$). For the variable visit, participants recalled in total more words during the four blocks on Visit 1 ($M = 64.11$, $Sd = 12.01$) in comparison to Visit 2 ($M = 28.68$, $Sd = 12.99$). For condition, a pairwise comparison using a Bonferroni correction of multiple comparison revealed that sham stimulation ($M = 23.73$ $Sd = 14.33$) was significantly different from cathodal ($M = 31.12$, $Sd = 11.67$, F (1,78) = 6.66 $p = .012$) and anodal ($M = 31.70$, $Sd = 11.38$, F (1,78) = 10.07, $p = .002$) stimulation. No significant effect was obtained between cathodal and anodal stimulation. No significant interaction was obtained between condition x area (F (2,78) = 2.65, $p = .077$), visit x condition (F (2,78) = 0.42, $p = .66$) and visit x area (F (2,78) = 4.24, $p = .082$). Finally, a significant interaction between visit x condition x area (F (2,78) = 3.77,

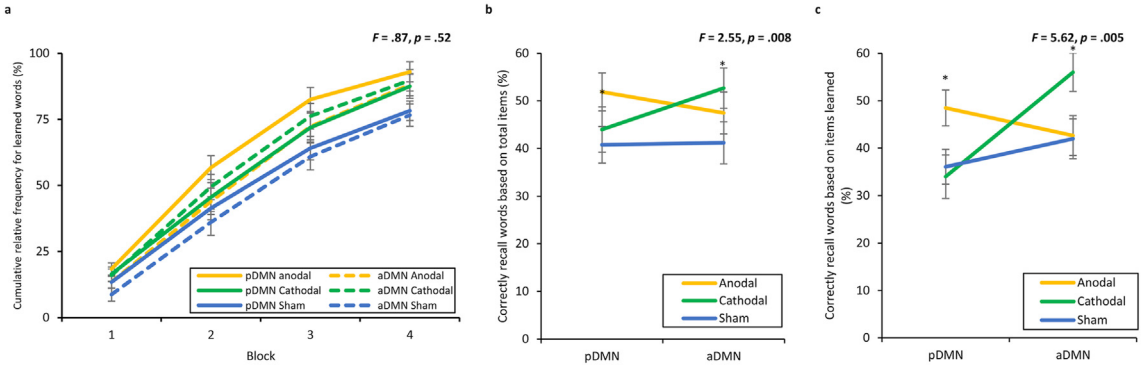

Fig. 2. (a) Cumulative learning curve of the percentage of words learned over the 4 study blocks on Visit 1 in the different combinations of target regions and stimulation groups. Percentage of words correctly recalled in the different combinations of target regions and stimulation groups – (b) A comparison on how many words participants correctly retrieved during Visit 2 between participtants that received aDMN or pDMN HD-tDCS based on total number of word-pairs presented during Visit 1 (i.e. 75) (c) A comparison on how many words participants correctly retrieved during Visit 2 between participants that received aDMN or pDMN HD-tDCS based on total number of word-pairs learned during Visit 1. Error bars represent standard errors of the mean.

$p = .027$) was obtained. For Visit 1, no significant effect was obtained when comparing, anodal, cathodal and sham stimulation for targeting pDMN or aDMN. For Visit 2, a simple contrast analysis revealed that significantly more words were recalled for the anodal stimulation targeting the pDMN in comparison to cathodal $F(1,78) = 6.26$, $p = .014$) and sham stimulation $F(1,78) = 7.26$, $p = .009$). No significant difference was obtained between cathodal and sham stimulation $F(1,78) = 0.01$, $p = .92$). For stimulation targeting aDMN, a simple contrast analysis revealed that significantly more words were recalled for the cathodal stimulation in comparison to anodal $F(1,78) = 3.99$, $p = .049$) and sham stimulation $F(1,78) = 8.11$, $p = .006$). No significant difference was obtained between anodal and sham stimulation $F(1,78) = 0.71$, $p = .40$). See Fig. 3 for summary.

Control variables

1. POMS Questionnaire Analysis

A repeated measures ANOVA with POMS scores (before vs. after stimulation) as within-subjects variable, area (aDMN vs. pDMN) and condition (anodal vs. cathodal vs. sham) as between-subjects variables showed a non-significant interaction effect ($F(2,78) = 0.06$, $p = .94$). These results suggest that stimulation has no significant effect on overall mood change regardless of the stimulation conditions and locations. See Fig. 4 for overview.

2. tDCS side effects

No major adverse events were reported. A MANOVA including area (aDMN vs. pDMN) x condition (anodal vs. cathodal vs. sham) did not reveal a significant interaction effect ($F(20,140) = 0.90$, $p = .58$) indicating the stimulation did not obtain a difference in side effects in relationship to area or stimulation condition. Our results indicate that the stimulation was well tolerated, and no stimulation-related complications were noted by participants or experimenters during the HD-tDCS procedure. See Fig. 5 for overview.

3. Stimulation Condition blindness

For pDMN ($\chi^2(2) = 1.88$, $p = .40$) and aDMN ($\chi^2(2) = 2.35$, $p = .31$), a χ^2 analysis did not show a significant effect for the expected stimulation and the actually received stimulation. See Fig. 6 for overview.

Discussion

Our study demonstrates that HD-tDCS can enhance memory retrieval up to seven days after learning a word-association task. This effect is target and stimulation specific. That is, anodal HD-tDCS targeting the pDMN during retrieval improves memory retrieval in comparison to sham or cathodal stimulation. For the aDMN, cathodal HD-tDCS during retrieval improves memory retrieval in comparison to sham or anodal stimulation. Our results revealed that all groups learned the same amount of words on average during the word-association task on the first visit, but participants that received anodal HD-tDCS targeting the pDMN or cathodal HD-tDCS targeting the aDMN during the second visit (i.e., seven days after learning the task) were able to perform better in comparison to the control conditions. Our analysis further revealed that the memory effect obtained is present when corrected for the number of words participants learned during the first visit or the total amount of words presented.

The results from the current study provide evidence for a functional dissociation in the DMN during remote memory retrieval as suggested by some previous studies [18,19]. There is an ongoing debate about the mechanism of action of anodal and cathodal stimulation. Studies examining changes in the motor cortex consistently report that anodal/cathodal stimulation increases/decreases underlying activity inducing long-term potentiation or long-term depression [27–29,40]. Yet other studiwswhere no able to replicate that anodal stimulation increases excitability in the over the motor cortex or that it is parameter specific [41,42]. However, a meta-analysis of non-motor cortex studies revealed that anodal-excitation is more consistent than cathodal-inhibition [31]. In addition, several beneficial effects of cathodal tDCS on cognitive tasks such as distant disinhibition, reduction of distractive network activity, improvement of signal-to-noise ratio, and noise filtering have been proposed [43,44]. From these studies, it is possible to hypothesize that the anodal/cathodal stimulation of the pDMN/aDMN may follow different mechanisms of action (which can be determined by future neuroimaging studies) but ultimately lead to a functional dissociation in the DMN during memory retrieval.

Anatomically, the pDMN and aDMN are connected to the medial temporal regions through direct and indirect connections [45,46].

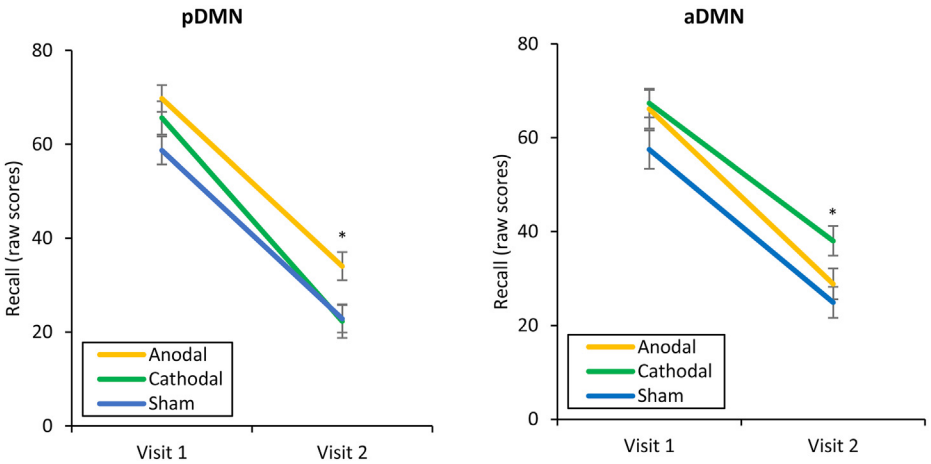

Fig. 3. Recalled number of words (raw scores) for Visit 1 (cumulative) and Visit 2 as with-in subjects factor for stimulation area (aDMN, pDMN) and stimulation condition (anodal, cathodal, sham) as between-subjects factors. Error bars represent standard errors of the mean.

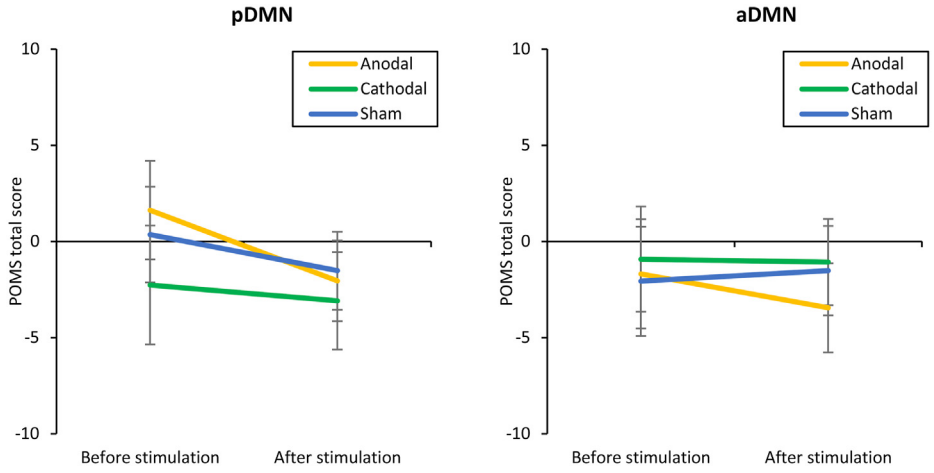

Fig. 4. The bar charts represent the pre-POMS vs post-POMS score between three different stimulation conditions (anodal, cathodal, and sham) for pDMN and aDMN. Error bars represent standard errors of the mean.

Functionally, the role of pDMN in memory retrieval is more concrete as seen by different functional imaging and electrophysiological studies showing increased connectivity with the medial temporal regions and successful retrieval [9,11,47,48]. It is reasonable to hypothesize anodal pDMN stimulation improves memory retrieval by increasing activity in pDMN and its connectivity with MTL as the potential underlying neuromechanism. However, the role of the aDMN is not clear. It is debatable whether aDMN is involved in the learning, consolidation or retrieval of long-term memories. Inactivation of mPFC leads to deficits in retrieval of remote memories while leaving recent memory intact, as seen in different tasks including the radial arm maze [49], Morris water maze [50], contextual fear conditioning [51,52], and conditioned taste aversion [53] in animal models. Some studies also argue that as time passes, memories are stored by stable neocortical networks such as the aDMN rather than in the hippocampus [49,54,55]. In rats, this has been shown after 30 and 200 days [56] but the cut-off for humans is still unclear [54].

In the current study, we show that aDMN is actively involved in retrieval of long-term memories, one week after the learning phase. We know that decoupling the aDMN from the rest of the network aids in successful retrieval [19]. Hence, it is possible that cathodal stimulation maybe aiding this decoupling. A HD-tDCS setup, similar to our aDMN stimulation, that targets the dorsal anterior cingulate

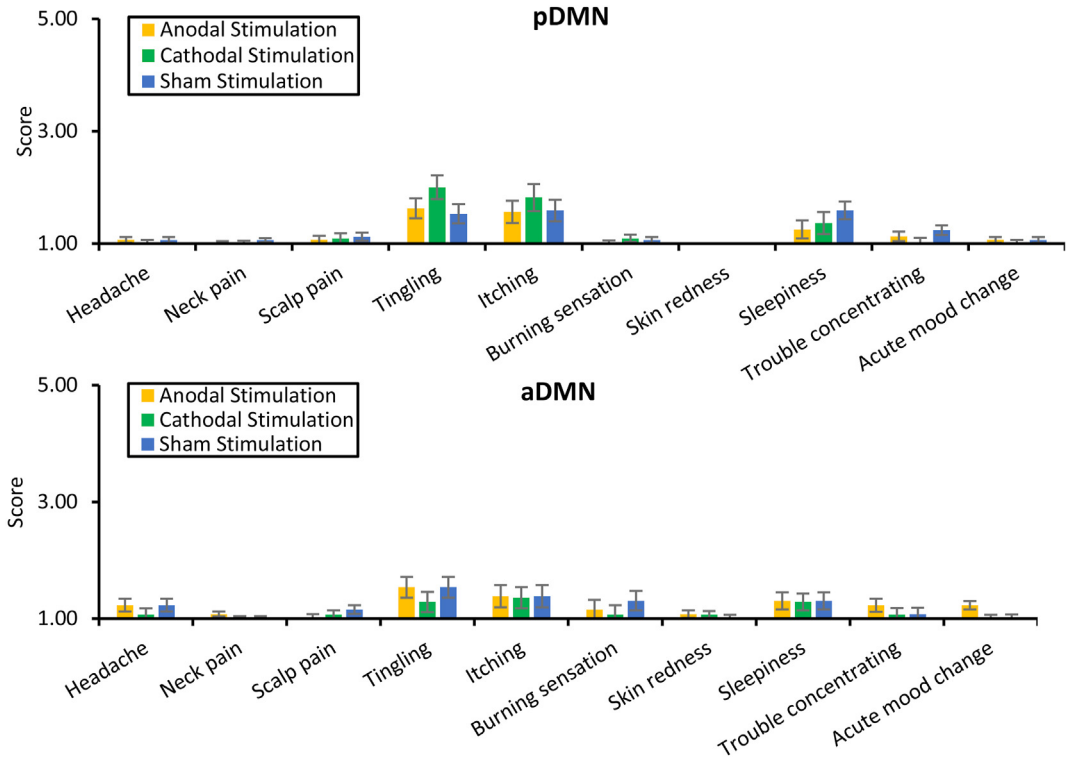

Fig. 5. Bar chart represents the mean scores on different tDCS related side effects on different stimulation condition (anodal, cathodal, and sham) for pDMN and aDMN. Error bars represent standard errors of the mean.

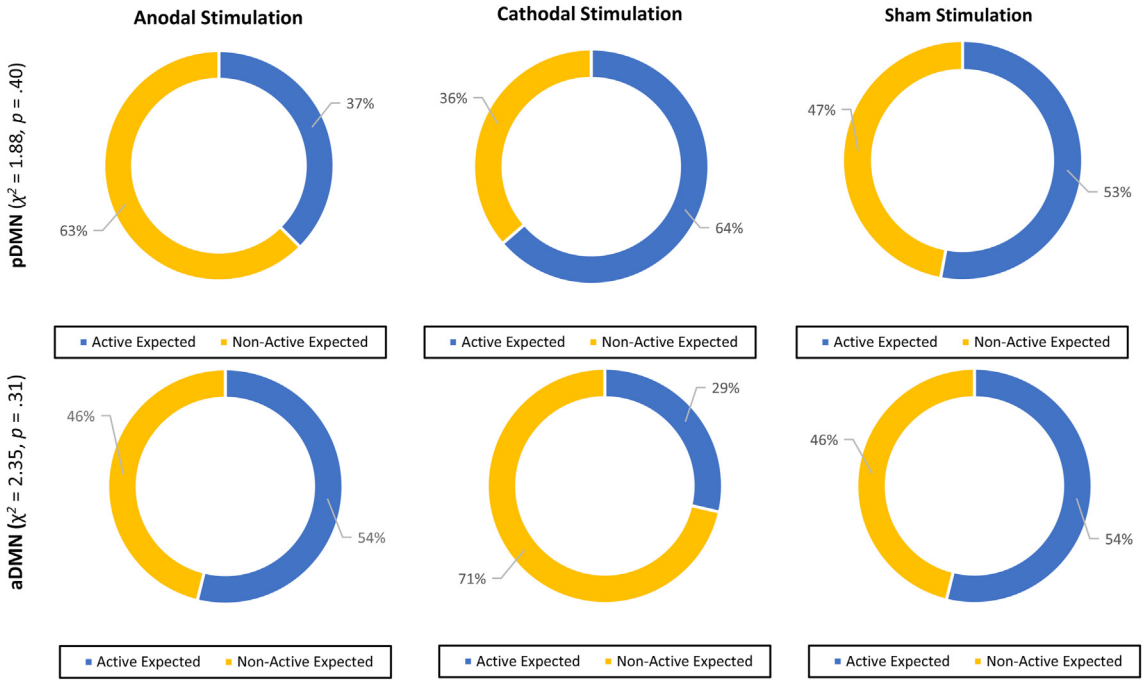

Fig. 6. The pie charts represent the proportion of subjects who guessed either they were received active or sham stimulation for different stimulation condition (anodal, cathodal, and sham) targeting pDMN and aDMN.

cortex (dACC) found increase in theta activity in the targeted region [57] which goes together with decreased BOLD signal in the DMN [58]. Also, a causal increase in theta activity in the aDMN prior to that in the hippocampus results in successful memory retrieval [59]. It is possible that within this one week the hippocampus may still be important to the retrieval process and cathodal aDMN stimulation may be improving the communication between these two regions aiding the retrieval. The possibility of tDCS-induced changes in connectivity between the MTL and DMN through polarity-specific HD-tDCS agrees with the idea of synaptic strengthening being one of the primary explanations of memory retrieval [1]. This way, we may be increasing this synaptic strength through HD-tDCS thereby unsilencing previously formed neuronal connections to aid long-term retrieval similar to what was done with optogentics in mice [1]. This dissociation within DMN during memory retrieval also aligns with the consistant findings of fractionations based on resting-state fMRI connectivity analyses [60–62]. Specifically, the resting-state connectivity patteren of mPFC and PCC exhibit a dissociation along the anterior-posterior axis [62]. This anticorrelation combined with the beneficial effect of cathodal stimulation in distant disinhibition [43,63], it is possible that cathodal aDMN stimulation inadvertently activates the pDMN which resembles the effects from anodal pDMN stimulation and eventually boosted memory retrieval.

The current study also sets up future implications for therapeutic treatment targets for patients with cognitive decline. Research reveals a functional degradation of the pDMN using fMRI in patients with MCI on an episodic memory retrieval test compared to the healthy control group [64]. The pDMN is also particularly vulnerable to early deposition of amyloid β-protein, one of the biomarkers of AD, in both AD patients and in elderly people without dementia [65]. On the contrary, amnestic MCI patients exhibit increased activity in the aDMN shown by resting-state fMRI [66]. By applying the anodal-excitation, cathodal-inhibition theory to the current study, we can predict that anodal stimulation of the pDMN and cathodal stimulation of the aDMN could help improve memory deficits in patient populations. This reflects on the idea that in amnestic individuals, memories may remain intact in engram cells, but retrieval of memories is impaired and that increased synaptic strength through stimulation of engrams can improve long-term retrieval in amnesia [1]. Thus the current study lays the foundation of exploring polarity-dependent HD-tDCS for improving memory retrieval in amnestic adults as a treatment for memory decline.

For the first time, our results show a causal relationship between memory retrieval and polarity-specific HD-tDCS stimulation of aDMN and pDMN suggesting improved synaptic strength between the DMN and MTL as a possible underlying neuromechanism. Yet, due to lack of supporting data and the inconsistent findings of aDMN in memory retrieval from previous studies, further research is needed. It is also possible that cathodal aDMN stimulation could decouple aDMN from the rest of DMN or distanly disinhibit pDMN thereby mirroring the effect of anodal pDMN stimulation thereby facilitating memory retrieval. Additionally, our results support the idea of cathodal stimulation in non-motor regions while performing cognitive tasks will not always impair task performance. In conclusion, the current study could inspire future research to investigate (1) the neural mechanism underlying polarity-specific DMN stimulation during memory retrieval, (2) time-dependent way of stimulating the aDMN and pDMN and studying its effects on neural and behavioural correlates of memory retrieval, and (3) stimulation effects on patient populations who suffer from impaired memory function.

Conclusion

The current study using non-invasive HD-tDCS of the aDMN and pDMN shows that anodal stimulation of the pDMN and cathodal stimulation of the aDMN increases memory retrieval performance one week after the learning phase. To the best of our knowledge, this is the first study to be able to convey a possible causal relationship between activity in the DMN and episodic memory

retrieval. Future research is needed to better understand the neural mechanisms and the potential application in a patient population.

Declaration of interest

The authors declare no conflict of interest.

CRediT authorship contribution statement

Yuefeng Huang: Data collection, Formal analysis, Project administration, Software, Writing – original draft, VisualizationVisualisation. **Anusha Mohan:** Formal analysis, Writing – original draft. **S. Lauren McLeod:** Data curation, VisualizationVisualisation, Investigation. **Alison M. Luckey:** Validation, Writing – review & editing. **John Hart:** Medical Supervision. **Sven Vanneste:** Conceptualization, Supervision, Methodology, Writing, Resources.

References

[1] Tonegawa S, Pignatelli M, Roy DS, Ryan TJ. Memory engram storage and retrieval. Curr Opin Neurobiol 2015;35:101–9.
[2] Ryan TJ, Roy DS, Pignatelli M, Arons A, Tonegawa S. Engram cells retain memory under retrograde amnesia. Science 2015;348(6238):1007–13.
[3] Ritchey M, Cooper RA. Deconstructing the posterior medial episodic network. Trends Cognit Sci 2020;24(6):451–65.
[4] Huang Y, Hullfish J, De Ridder D, Vanneste S. Meta-analysis of functional subdivisions within human posteromedial cortex. Brain Struct Funct 2019;224(1):435–52.
[5] Buckner RL, DiNicola LM. The brain's default network: updated anatomy, physiology and evolving insights. Nat Rev Neurosci 2019;20(10):593–608.
[6] Xu X, Yuan H, Lei X. Activation and connectivity within the default mode network contribute independently to future-oriented thought. Sci Rep 2016;6:21001.
[7] Damoiseaux JS, Beckmann CF, Arigita EJS, Barkhof F, Scheltens P, Stam CJ, et al. Reduced resting-state brain activity in the “default network” in normal aging. Cerebr Cortex 2007;18(8):1856–64.
[8] Lei X, Zhao Z, Chen H. Extraversion is encoded by scale-free dynamics of default mode network. Neuroimage 2013;74:52–7.
[9] Huijbers W, Vannini P, Sperling RA, C M P, Cabeza R, Daselaar SM. Explaining the encoding/retrieval flip: memory-related deactivations and activations in the posteromedial cortex. Neuropsychologia 2012;50(14):3764–74.
[10] Maguire EA, Mummery CJ. Differential modulation of a common memory retrieval network revealed by positron emission tomography. Hippocampus 1999;9(1):54–61.
[11] Lega B, Germi J, Rugg MD. Modulation of oscillatory power and connectivity in the human posterior cingulate cortex supports the encoding and retrieval of episodic memories. J Cognit Neurosci 2017;29(8):1415–32.
[12] Rugg MD, Vilberg KL. Brain networks underlying episodic memory retrieval. Curr Opin Neurobiol 2013;23(2):255–60.
[13] Vilberg KL, Rugg MD. Memory retrieval and the parietal cortex: a review of evidence from a dual-process perspective. Neuropsychologia 2008;46(7):1787–99.
[14] Tonegawa S, Morrissey MD, Kitamura T. The role of engram cells in the systems consolidation of memory. Nat Rev Neurosci 2018;19(8):485–98.
[15] Cabeza R, Prince SE, Daselaar SM, Greenberg DL, Budde M, Dolcos F, et al. Brain activity during episodic retrieval of autobiographical and laboratory events: an fMRI study using a novel photo paradigm. J Cognit Neurosci 2004;16(9):1583–94.
[16] Svoboda E, McKinnon MC, Levine B. The functional neuroanatomy of autobiographical memory: a meta-analysis. Neuropsychologia 2006;44(12):2189–208.
[17] McDermott KB, Szpunar KK, Christ SE. Laboratory-based and autobiographical retrieval tasks differ substantially in their neural substrates. Neuropsychologia 2009;47(11):2290–8.
[18] Sestieri C, Corbetta M, Romani GL, Shulman GL. Episodic memory retrieval, parietal cortex, and the default mode network: functional and topographic analyses. J Neurosci : Off J Soc Neurosci 2011;31(12):4407–20.
[19] Müller NC, Dresler M, Janzen G, Beckmann CF, Fernandez G, Kohn N. Medial prefrontal decoupling from the default mode network benefits memory. Neuroimage 2020;210:116543.
[20] Leong SL, De Ridder D, Vanneste S, Sutherland W, Ross S, Manning P. High definition transcranial pink noise stimulation of anterior cingulate cortex on food craving: an explorative study. Appetite 2018;120:673–8.
[21] Kuo HI, Bikson M, Datta A, Minhas P, Paulus W, Kuo MF, et al. Comparing cortical plasticity induced by conventional and high-definition 4 x 1 ring tDCS: a neurophysiological study. Brain stimulation 2013;6(4):644–8.
[22] Datta A, Bansal V, Diaz J, Patel J, Reato D, Bikson M. Gyri-precise head model of transcranial direct current stimulation: improved spatial focality using a ring electrode versus conventional rectangular pad. Brain stimulation 2009;2(4):201–7. 7 e1.
[23] To WT, Hart J, De Ridder D, Vanneste S. Considering the influence of stimulation parameters on the effect of conventional and high-definition transcranial direct current stimulation. Expet Rev Med Dev 2016;13(4):391–404.
[24] Liu A, Voroslakos M, Kronberg G, Henin S, Krause MR, Huang Y, et al. Immediate neurophysiological effects of transcranial electrical stimulation. Nat Commun 2018;9(1):5092.
[25] Bikson M, Inoue M, Akiyama H, Deans JK, Fox JE, Miyakawa H, et al. Effects of uniform extracellular DC electric fields on excitability in rat hippocampal slices in vitro. J Physiol 2004;557(Pt 1):175–90.
[26] Rahman A, Reato D, Arlotti M, Gasca F, Datta A, Parra LC, et al. Cellular effects of acute direct current stimulation: somatic and synaptic terminal effects. J Physiol 2013;591(10):2563–78.
[27] Amadi U, Ilie A, Johansen-Berg H, Stagg CJ. Polarity-specific effects of motor transcranial direct current stimulation on fMRI resting state networks. Neuroimage 2014;88:155–61.
[28] Stagg CJ, Antal A, Nitsche MA. Physiology of transcranial direct current stimulation. J ECT 2018;34(3):144–52.
[29] Stagg CJ, Best JG, Stephenson MC, O'Shea J, Wylezinska M, Kincses ZT, et al. Polarity-sensitive modulation of cortical neurotransmitters by transcranial stimulation. J Neurosci 2009;29(16):5202–6.
[30] Edwards D, Cortes M, Datta A, Minhas P, Wassermann EM, Bikson M. Physiological and modeling evidence for focal transcranial electrical brain stimulation in humans: a basis for high-definition tDCS. Neuroimage 2013;74:266–75.
[31] Jacobson L, Koslowsky M, Lavidor M. tDCS polarity effects in motor and cognitive domains: a meta-analytical review. Exp Brain Res 2012;216(1):1–10.
[32] Podda MV, Cocco S, Mastrodonato A, Fusco S, Leone L, Barbati SA, et al. Anodal transcranial direct current stimulation boosts synaptic plasticity and memory in mice via epigenetic regulation of Bdnf expression. Sci Rep 2016;6:22180.
[33] Mancini M, Brignani D, Conforto S, Mauri P, Miniussi C, Pellicciari MC. Assessing cortical synchronization during transcranial direct current stimulation: a graph-theoretical analysis. Neuroimage 2016;140:57–65.
[34] Vanneste S, Mohan A, Yoo HB, Huang Y, Luckey AM, McLeod SL, et al. The peripheral effect of direct current stimulation on brain circuits involving memory. Sci Adv 2020;6(45).
[35] Nelson TO, Dunlosky J. Norms of paired-associate recall during multitrial learning of Swahili-English translation equivalents. Memory 1994;2(3):325–35.
[36] Karpicke JD, Roediger 3rd HL. The critical importance of retrieval for learning. Science 2008;319(5865):966–8.
[37] Brunoni AR, Amadera J, Berbel B, Volz MS, Rizzerio BG, Fregni F. A systematic review on reporting and assessment of adverse effects associated with transcranial direct current stimulation. Int J Neuropsychopharmacol 2011;14(8):1133–45.
[38] Huang Y, Datta A, Bikson M, Parra LC. Realistic vOlumetric-Approach to Simulate Transcranial Electric Stimulation – ROAST – a fully automated open-source pipeline. J Neural Eng 2019;16(5):1–15.
[39] Grabner G, Janke AL, Budge MM, Smith D, Pruessner J, Collins DL. Symmetric atlasing and model based segmentation: an application to the hippocampus in older adults. Medical image computing and computer-assisted intervention. MICCAI International Conference on Medical Image Computing and Computer-Assisted Intervention 2006;9(Pt 2):58–66.
[40] Nitsche MA, Paulus W. Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation. J Physiol 2000;527(3):633–9.
[41] Jonker ZD, Gaiser C, Tulen JHM, Ribbers GM, Frens MA, Selles RW. No effect of anodal tDCS on motor cortical excitability and no evidence for responders in a large double-blind placebo-controlled trial. Brain stimulation 2021;14(1):100–9.
[42] Agboada D, Mosayebi Samani M, Jamil A, Kuo MF, Nitsche MA. Expanding the parameter space of anodal transcranial direct current stimulation of the primary motor cortex. Sci Rep 2019;9(1):18185.
[43] Schroeder PA, Plewnia C. Beneficial effects of cathodal transcranial direct current stimulation (tDCS) on cognitive performance. Journal of Cognitive Enhancement 2017;1(1):5–9.
[44] Weiss M, Lavidor M. When less is more: evidence for a facilitative cathodal tDCS effect in attentional abilities. J Cognit Neurosci 2012;24(9):1826–33.
[45] Bubb EJ, Metzler-Baddeley C, Aggleton JP. The cingulum bundle: anatomy, function, and dysfunction. Neurosci Biobehav Rev 2018;92:104–27.
[46] Eichenbaum H. Prefrontal–hippocampal interactions in episodic memory. Nat Rev Neurosci 2017;18(9):547–58.
[47] Lin JJ, Umbach G, Rugg MD, Lega B. Gamma oscillations during episodic memory processing provide evidence for functional specialization in the longitudinal axis of the human hippocampus. Hippocampus 2019;29(2):68–72.
[48] Ren Y, Nguyen VT, Sonkusare S, Lv J, Pang T, Guo L, et al. Effective connectivity of the anterior hippocampus predicts recollection confidence during natural memory retrieval. Nat Commun 2018;9(1):4875.
[49] Maviel T, Durkin TP, Menzaghi F, Bontempi B. Sites of neocortical reorganization critical for remote spatial memory. Science 2004;305(5680):96–9.

[50] Teixeira CM, Pomedli SR, Maei HR, Kee N, Frankland PW. Involvement of the anterior cingulate cortex in the expression of remote spatial memory. J Neurosci 2006;26(29):7555–64.
[51] Frankland PW, Bontempi B, Talton LE, Kaczmarek L, Silva AJ. The involvement of the anterior cingulate cortex in remote contextual fear memory. Science 2004;304(5672):881–3.
[52] Holahan MR, Routtenberg A. Post-translational synaptic protein modification as substrate for long-lasting, remote memory: an initial test. Hippocampus 2007;17(2):93–7.
[53] Ding HK, Teixeira CM, Frankland PW. Inactivation of the anterior cingulate cortex blocks expression of remote, but not recent, conditioned taste aversion memory. Learn Mem 2008;15(5):290–3.
[54] Takashima A, Petersson KM, Rutters F, Tendolkar I, Jensen O, Zwarts M, et al. Declarative memory consolidation in humans: a prospective functional magnetic resonance imaging study. Proc Natl Acad Sci Unit States Am 2006;103(3):756–61.
[55] Takehara K, Kawahara S, Kirino Y. Time-dependent reorganization of the brain components underlying memory retention in trace eyeblink conditioning. J Neurosci 2003;23(30):9897–905.
[56] Quinn JJ, Ma QD, Tinsley MR, Koch C, Fanselow MS. Inverse temporal contributions of the dorsal hippocampus and medial prefrontal cortex to the expression of long-term fear memories. Learn Mem 2008;15(5):368–72.
[57] To WT, Eroh J, Hart J, Vanneste S. Exploring the effects of anodal and cathodal high definition transcranial direct current stimulation targeting the dorsal anterior cingulate cortex. Sci Rep 2018;8(1):1–16.
[58] Scheeringa R, Bastiaansen MC, Petersson KM, Oostenveld R, Norris DG, Hagoort P. Frontal theta EEG activity correlates negatively with the default mode network in resting state. Int J Psychophysiol 2008;67(3):242–51.
[59] Place R, Farovik A, Brockmann M, Eichenbaum H. Bidirectional prefrontal-hippocampal interactions support context-guided memory. Nat Neurosci 2016;19(8):992–4.
[60] Buckner RL, Andrews-Hanna JR, Schacter DL. The brain's default network: anatomy, function, and relevance to disease. Ann N Y Acad Sci 2008;1124:1–38.
[61] Meunier D, Lambiotte R, Fornito A, Ersche KD, Bullmore ET. Hierarchical modularity in human brain functional networks. Front Neuroinf 2009;3:37.
[62] Uddin LQ, Kelly AM, Biswal BB, Castellanos FX, Milham MP. Functional connectivity of default mode network components: correlation, anticorrelation, and causality. Hum Brain Mapp 2009;30(2):625–37.
[63] Pope PA, Miall RC. Task-specific facilitation of cognition by cathodal transcranial direct current stimulation of the cerebellum. Brain stimulation 2012;5(2):84–94.
[64] Ries ML, Schmitz TW, Kawahara TN, Torgerson BM, Trivedi MA, Johnson SC. Task-dependent posterior cingulate activation in mild cognitive impairment. Neuroimage 2006;29(2):485–92.
[65] Sperling RA, Laviolette PS, O'Keefe K, O'Brien J, Rentz DM, Pihlajamaki M, et al. Amyloid deposition is associated with impaired default network function in older persons without dementia. Neuron 2009;63(2):178–88.
[66] Jin M, Pelak VS, Cordes D. Aberrant default mode network in subjects with amnestic mild cognitive impairment using resting-state functional MRI. Magn Reson Imaging 2012;30(1):48–61.
[67] American Electroencephalographic Society guidelines for standard electrode position nomenclature. J Clin Neurophysiol 1991;8(2):200–2.