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Original Article

The left prefrontal cortex determines relevance at encoding and governs episodic memory formation

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The role hemispheric lateralization in the prefrontal cortex plays for episodic memory formation in general, and for emotionally valenced information in particular, is debated. In a randomized, double-blind, and sham-controlled design, healthy young participants ($n = 254$) performed 2 runs of encoding to categorize the perceptual, semantic, or emotionally valenced (positive or negative) features of words followed by a free recall and a recognition task. To resolve competing hypotheses about the contribution of each hemisphere, we modulated left or right dorsolateral prefrontal cortex (DLPFC) activity using transcranial direct current stimulation during encoding (1 mA, 20 min). With stimulation of the left DLPFC, but not the right DLPFC, encoding and free recall performance improved particularly for words that were processed semantically. In addition, enhancing left DLPFC activity increased memory formation for positive content while reducing that for negative content. In contrast, promoting right DLPFC activity increased memory formation for negative content. The left DLPFC assesses semantic properties of new memory content at encoding and thus influences how successful new episodic memories are established. Hemispheric laterlization—more active left DLPFC and less active right DLPFC—at the encoding stage shifts the formation of memory traces in favor of positively valenced content.

Key words: tDCS; level of processing; incidental learning; episodic memory; emotional valence; DLPFC; alertness.

Introduction

It is common knowledge that what matters most to us we do remember best. The formation of episodic memory depends on how the information to be remembered is processed at the encoding stage. The "level of encoding" framework postulates that deeper encoding benefits later retrieval (Craik and Lockhart 1972; Craik and Tulving 1975), and that the retrieval can be further facilitated when information is emotionally valenced (Ferré et al. 2015). At a neuronal level, a process-specific lateralization model has been suggested for the formation of new episodic memories. The model posits that the left prefrontal cortex is predominantly involved during memory encoding, whereas the right prefrontal cortex is more active during retrieval (at least in healthy young adults) (Tulving et al. 1994; Habib et al. 2003). A differential contribution of each hemisphere has also been proposed for processing of emotionally valenced content. According to the "valence specific hypothesis" and the "approach avoidance hypothesis," the left hemisphere processes positive or approach-related content and the right hemisphere negative or withdrawal-related content (Ahern and Schwartz 1979; Davidson 1992, 1995). Alternatively, according to the "right hemisphere hypothesis," the right hemisphere processes all emotional content, regardless of its valence (Borod et al. 1998).

In the context of episodic memory formation, it is important to have a clear understanding of the differential role left, or right prefrontal cortex activity has in general, and during emotional processing in particular. This can help to develop further current models of prefrontal cortex lateralization in health, and consequently, predict what goes wrong in diseases (e.g. mood disorders). To this end, modulating left or right prefrontal activity at encoding or retrieval can provide dynamic insights. Lesion studies indicate that the left dorsolateral prefrontal cortex (DLPFC) plays a critical role in processes based on cognitive control as well as in semantic and lexical word processing, while the right DLPFC contributes to attention and when complex behaviors require decision making (Barbey et al. 2013; Riès et al. 2016; Bartolomeo and Seidel 2019). A direct comparison of left or right

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DLPFC inhibition with noninvasive brain stimulation in young healthy adults revealed that inhibiting the left DLPFC during encoding or inhibiting the right DLPFC during recognition reduced retrieval performance (Rossi et al. 2001; Sandrini et al. 2003; Manenti et al. 2010). However, these studies with small cohorts did not differentiate effects at encoding from those at retrieval. Thus, the effects of differential DLPFC modulation at encoding remain less well understood, and it is important to complement insight into the effects of DLPFC inhibition with knowledge about what happens when DLPFC activity is enhanced. In addition, one needs to know whether DLPFC activity influences episodic memory formation in general or depending on the emotional content of the information to be encoded. To answer these questions, we modulated left or right DLPFC activity at encoding in a large cohort of healthy young individuals during an incidental learning task with 3 depths of encoding (shallow, deep, and emotional), as this allows investigating encoding of information in general, encoding of emotionally valenced content, and episodic memory formation.

We hypothesized that boosting left DLPFC function at encoding would enhance episodic memory formation, while promoting right DLPFC activity would not. In addition, we hypothesized that stimulating the left or right DLPFC would differentially modulate processing (and consequently retrieval) of emotionally valenced content. If the "valence specific hypothesis" or the "approach avoidance hypothesis" held true we would expect to see an increase in positively valenced processing and retrieval when stimulating the left DLPFC and an increase in negatively valenced processing and retrieval when stimulating the right DLPFC. If the "right hemisphere hypothesis" held true, we would expect to find an increase in both positively and negatively processed content only with stimulation of the right DLPFC.

Material and methods

Participants

We recruited 287 healthy, right-handed individuals via flyers circulated at Freiburg or Bern University. Of these, $n = 29$ did not meet inclusion criteria and $n = 4$ indicated that they were aware of the learning situation. Thus, $n = 254$ individuals (23.3 ± 2.8 years of age, range 20–31; Table 1) were finally included in the study. All participants gave written informed consent and received financial compensation or course credit. The Ethics Committee of Freiburg University or the Cantonal Ethics Committee of Bern approved the study. The study conformed to the Declaration of Helsinki.

Inclusion and exclusion criteria

The study followed a standardized protocol at both sites. Participants had to be fluent in German, right-handers, nonsmokers, with normal or corrected-to-normal vision and no history of psychiatric/neurological disorders. Further exclusion criteria were any history of seizures, current use of psychotropic medication, skin disorders, alcohol/drug abuse or addiction, brain damage, tinnitus, magnetized implants (e.g. cardiac pacemaker), or pregnancy. Handedness was assessed using the Edinburgh-Handedness-Inventory (Oldfield 1971). Symptoms of depression were assessed with Beck's Depression-Inventory-II (Beck et al. 1996), and we included participants with a BDI-II score ≤ 13.

On the day of the experiment, the participants were asked about how many hours they had slept the night before and how they rated the quality of sleep followed by a German verbal intelligence test (Schmidt and Metzler 1992) and the assessment of their current mood (Crawford and Henry 2004).

Transcranial direct current stimulation

We applied anodal transcranial direct current stimulation (tDCS) with a DC-plus stimulator device (Neuroconn GmbH, Ilmenau, Germany) that delivered direct current with an intensity of 1 mA. Anodal tDCS is thought to cause neural depolarization and thus enhance cortical excitability (Nitsche and Paulus 2000). We used 2 rubber electrodes (5×7 cm) coated with saline solution-soaked sponges to deliver the current to the scalp. Total current density did not exceed 0.03 mA/cm^2 and thus remained below safety limits (Poreisz et al. 2007).

Two different electrode montages were used: In Freiburg, we placed the anode over the left DLPFC at position F3 (Herwig et al. 2003) and, in Bern, over the right DLPFC at position F4 with the cathode always on the contralateral supraorbital region (Fig. 1A). Both experimenters (EN, CW) were trained (by JP) to ensure that the study was conducted according to its standardized protocol. We operated the device in "study mode," so that participants or investigator were unaware of the experimental condition. Participants were randomized to receive either sham or real tDCS (simple randomization by JP, who was not involved in data collection, allocation-ratio 1:1). We applied a sham condition at both study sites but since we were primarily interested in the difference between left and right DLPFC stimulation, we merged both sham groups for statistical analysis.

Real anodal tDCS consisted of a 15 s ramp-up phase followed by constant current at 1 mA for 20 min and then ramp-down for 15 s (Fig. 1B). For sham stimulation, the current was ramped up to a current of 1 mA just as in real tDCS but was then immediately ramped down again. This sham procedure produces similar sensations as real stimulation but without exerting any stimulation effects (Gandiga et al. 2006). At the end of the experiment, side effects, and the participants' perception of the stimulation condition were captured (Brunoni et al. 2011).

Incidental learning task

We used 80 nouns; that is, 40 words for encoding and an additional 40 for recognition (Woods et al. 2006;

Table 1. Sociodemographic characteristics of the sample. *Note:* M = mean, SD = standard deviation. Verbal intelligence was assessed with a vocabulary test. For the subjective ratings of sleep quality, a score of 0 denotes "very bad", while a score of 10 indicates "very good."

		Sham ($n = 126$)		Left DLPFC ($n = 64$)		Right DLPFC (n = 64)	
		M	SD	M	SD	M	SD
Shallow	Male/female (*n*)	18/24		10/11		9/11	
	Age (years)	23.55	2.98	23.86	2.71	22.80	3.25
	Verbal intelligence	102.07	5.17	103.9	4.18	104.83	5.24
	Hours of sleep	7.47	0.82	7.27	0.77	7.55	0.79
	Quality of sleep	7.49	1.86	7.35	1.69	7.53	1.39
Deep	Male/female (*n*)	23/19		11/11		11/13	
	Age (years)	22.64	2.47	24.18	2.04	22.75	2.94
	Verbal intelligence	102.81	4.14	105.09	5.99	105.76	5.66
	Hours of sleep	7.33	0.76	7.66	0.75	7.50	0.79
	Quality of sleep	7.17	2.10	7.17	1.63	7.29	1.60
Emotional	Male/female (*n*)	22/20		11/10		8/12	
	Age (years)	23.74	2.98	23.71	2.83	22.55	2.63
	Verbal intelligence	104.05	5.23	103.63	5.23	102.30	5.56
	Hours of sleep	7.35	0.97	6.88	0.78	7.38	0.81
	Quality of sleep	8.26	1.22	7.23	1.66	7.43	1.56

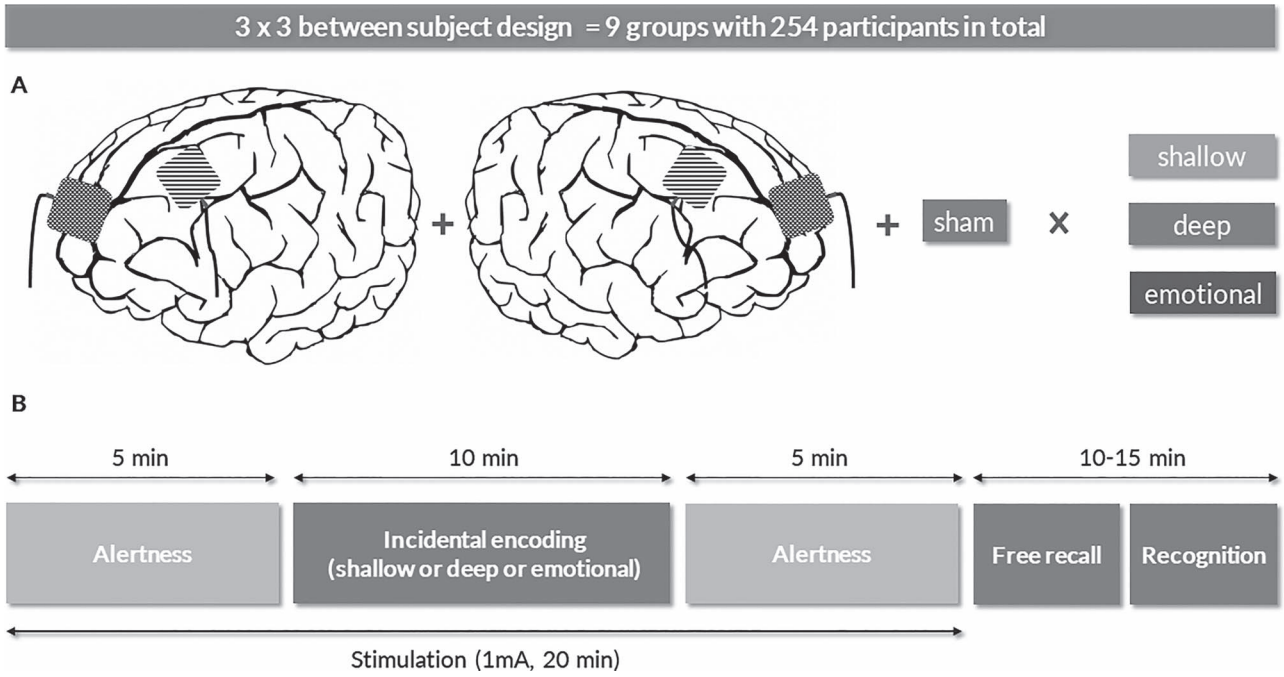

Fig. 1. Study design (A) and study procedure (B).

Herold 2008). During encoding, the words appeared on a computer screen in randomized order. Each word was presented until the participant responded with pressing a button. The time to the presentation of the next word was pseudorandomly jittered (0.5–2.5 s). Each group (shallow, deep, and emotional) performed 2 runs of encoding with the identical presentation of the 40 words but with different instructions (Fig. 2): In the shallow processing group, the participants had to indicate whether the word "contains an A" (first run) or whether the word "has exactly three syllables" (second run). Individuals in the deep processing group had to indicate whether the word was "animate" (first run) or denoted something "edible" (second run). In the emotional group, the participants had to indicate whether the word elicited "joy" (first run) or "fear" (second run) in them. Of the 40 words, 16 were targets (i.e. 8 targets in each run; target means that the correct decision for this word would be "yes"; e.g. "yes, the word contains an a"). The 16 target words for the emotional processing group had been rated to have an either positive or negative content in a previous study (Herold 2008).

Outcome measures of encoding performance were correct decisions (i.e. yes or no responses) and reaction times for these decisions. Outcome measures of free recall performance were the number of recalled targets (i.e.

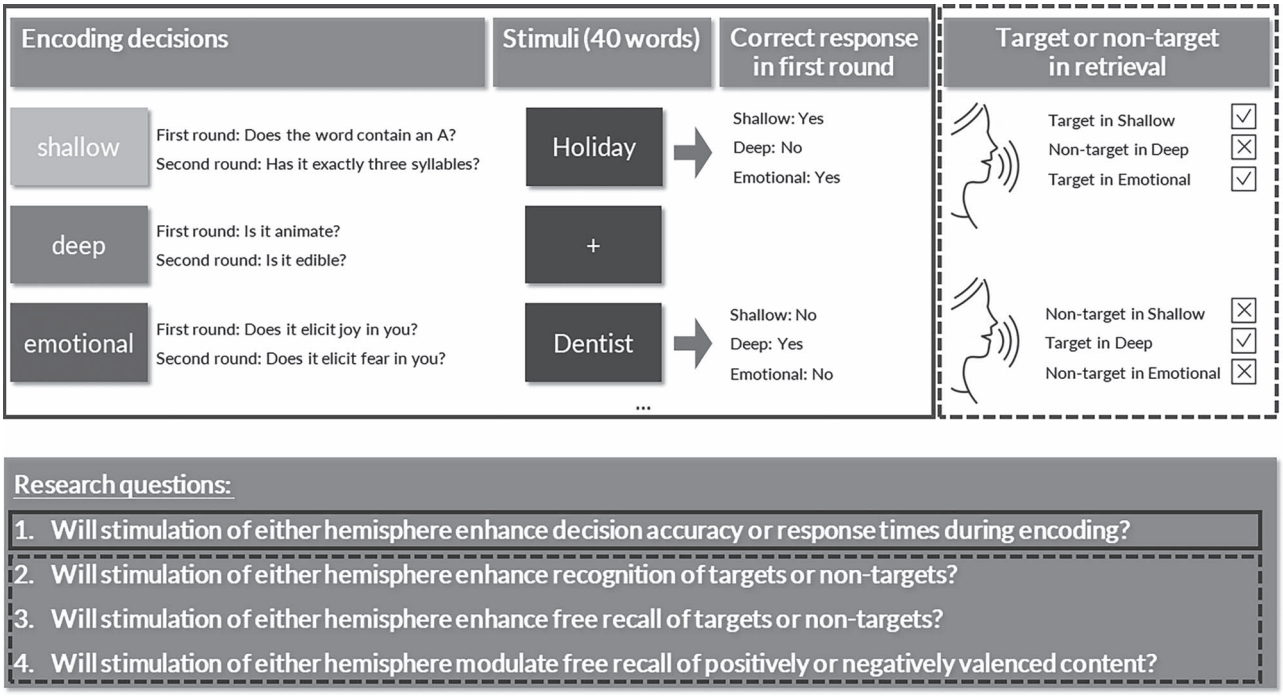

Fig. 2. Experimental set-up: incidental learning task with encoding (dark frame with solid line) and retrieval (dark frame with dashed line).

correct yes responses). We were particularly interested in targets, since previous research suggested that targets are recognized faster and remembered more easily than nontargets (Craik and Lockhart 1972; Craik and Tulving 1975). Determining whether a word is a target is easy for the shallow (or deep) processing group, because a word either contains an "A" (or is edible) or does not. The evaluation of emotional valence, however, is subject to greater variability between individuals, which makes it difficult to decide whether someone has correctly classified a word as positive (i.e. joyful) or negative (i.e. fearful). Therefore, we denoted targets in the emotional processing group by using the subjective rating (i.e. whether the participants answered with yes or no). Words that were classified as nontargets in the emotional processing group were classified as "neutral" since they elicited neither joy nor fear. Outcome measures for recognition performance were the number (and reaction times) of correctly recognized targets vs. nontargets.

Alertness task

We used an alertness task during which the participants were required to respond as fast as possible to the appearance of a single white cross on a black screen, either preceded by an auditory cue or not (i.e. phasic or intrinsic alertness). The interstimulus-interval between the auditory cue and the white cross was 0.6–1.5 s; the interstimulus-interval between each trial was 1.5–3.0 s. We used 2 blocks per condition and 20 trials in each block, resulting in 40 trials per condition.

Experimental design

In this double-blind, sham-controlled, and parallel group study, participants were randomly assigned to 1 of 9 groups in which either shallow, deep, or emotional processing of words was examined when participants were undergoing sham or real tDCS of the left or the right DLPFC (3 x 3 design; Fig. 1A). We programmed and presented stimuli with Presentation (Version 18.1, Neurobehavioral Systems, Inc., USA). The participants performed the task while sitting in front of a computer screen (diameter 14 inches) in a well-lit, quiet room. After electrode placement, real or sham tDCS was started together with the first block of an alertness task (Fig. 1B). The time this first block took (5 min) corresponded to the time it takes for tDCS to have an effect on cortical excitability (Nitsche and Paulus 2000) and gave the participants the opportunity to get used to the tingling sensation associated with the ramp-up phase. This was followed by 2 rounds of encoding using the incidental learning task. After encoding, the alertness task was presented again to reduce the recall advantage for later list items (i.e. recency effect) that would have occurred with immediate free recall (Schott et al. 2013). After this second alertness task, stimulation stopped. Then, we prompted participants to verbally report, in any order, as many words as possible from the list of words they had seen twice before (free recall). We enquired about the feelings associated with the free recall to test whether the free recall was unexpected (i.e. to ensure incidental learning). After free recall, we employed a recognition task, in which the participants were asked to indicate by button presses whether the word had been previously presented or not (Fig. 1B).

Statistical analysis

We first analyzed data acquired during encoding and then examined effects during retrieval (Fig. 2). More

specifically, we tested whether stimulation of either hemisphere enhanced encoding accuracy or response times. Thus, we examined whether targets or nontargets were detected faster or more accurately with stimulation of the left or right DLPFC in encoding run 1 or 2 (research question 1). We did not include the emotional processing group in this analysis because we used the subjective rating for the determination of emotional content so encoding accuracy would have been 100%. We next calculated whether targets or nontargets were recognized more accurately or faster during recognition with stimulation of the left or right DLPFC (research question 2). We then investigated whether targets or nontargets were remembered better at free recall with stimulation of the left or the right DLPFC (research question 3). For the emotional processing group, we additionally tested stimulation effects on positive, negative, or neutral content (research question 4).

For research question 1, we used mixed-model ANOVA for targets or nontargets with stimulation (real left, real right, sham) and encoding depth (shallow, deep, emotional) as between-subject factors and run (i.e. 1 and 2) as within-subject factor. For research question 2, 3, and 4, we applied multivariate ANOVA, each with stimulation (real left, real right, sham) and encoding depth (shallow, deep, emotional) as between-subject factors and the number of targets or nontargets as dependent variables (for research question 4, we used positive, negative, or neutral content as dependent variables).

For the alertness task, we again used mixed-model ANOVA, with encoding depth (shallow, deep, emotional) and stimulation condition (real left, real right, sham) as between-subject factors and time (i.e. before and after stimulation) as within-subject factor. We report univariate effects only in case of significant main effects or significant interactions.

We report analyses on the depths of encoding effects in the Supplementary Material.

We used SPSS (version 26.0; IBM Inc.; USA) for statistical analyses and GraphPad Prism (version 9.0.0; USA) for visualization of the results. Statistical significance levels were set to $P < 0.05$ (2-tailed). We adjusted for multiple comparisons using Tukey's method.

Results

All groups were similar in age, sex-ratio, verbal intelligence, and hours as well as quality of sleep in the night preceding the experiments (Table 1).

In addition, all participants were in an emotionally balanced mood state with a considerably higher positive than negative affect (Table 2). The participants tolerated the stimulation well. Tingling (82.4%), drowsiness (52.7%), itching (45.4%), and skin redness (45.0%) were most commonly reported and similar in the sham and real tDCS condition (Supplementary Table S1). When asked whether they thought they had sham or real tDCS, participants' responses were at chance level (Supplementary Table S2).

Encoding performance

Successful encoding is a prerequisite for later memory retrieval. Therefore, we first assessed whether stimulation of either DLPFC influenced encoding. We found a significant main effect of run ($F_{(2, 164)} = 11.20$, $P < 0.001$, $\eta^2 = 0.12$) and stimulation ($F_{(4, 330)} = 4.33$, $P = 0.02$, $\eta^2 = 0.03$). We also found a significant interaction between run and stimulation ($F_{(4, 330)} = 3.074$, $P = 0.02$, $\eta^2 = 0.04$) as well as run, stimulation, and encoding depths ($F_{(4, 330)} = 2.42$, $P = 0.04$, $\eta^2 = 0.03$). The runs were significantly different for targets ($F_{(1, 165)} = 22.16$, $P < 0.001$, $\eta^2 = 0.12$) but not nontargets. Depending on encoding depths ($F_{(2, 165)} = 3.79$, $P = 0.02$, $\eta^2 = 0.04$), stimulation had a significant effect only for target detection ($F_{(2, 165)} = 3.54$, $P = 0.02$, $\eta^2 = 0.04$), while there was a trend for nontargets ($F_{(2, 165)} = 2.54$, $P = 0.09$, $\eta^2 = 0.03$).

Posthoc tests revealed that only during the first encoding run, targets were detected significantly better with stimulation of the left DLPFC compared to both sham and right DLPFC stimulation in the deep processing group ($P < 0.05$, Fig. 3). In contrast, nontargets were detected significantly worse in the deep processing group with stimulation of the left DLPFC compared to right DLPFC stimulation ($P < 0.01$, Fig. 3). Stimulation had no significant effect on shallow processing, the second encoding run, or on reaction times in either run or group.

Recognition performance

We next examined whether stimulation given to either hemisphere modulated successful memory retrieval following encoding. Stimulation modulated reaction times during recognition (main effect of stimulation; $F_{(4, 480)} = 3.60$, $P = 0.007$, $\eta^2 = 0.03$) with improved reaction times to targets ($F_{(2, 240)} = 5.78$, $P = 0.004$, $\eta^2 = 0.05$) or to nontargets ($F_{(2, 240)} = 6.60$, $P = 0.002$, $\eta^2 = 0.05$). Posthoc tests revealed that with stimulation of the right DLPFC, targets ($P < 0.01$) or nontargets ($P < 0.01$) were recognized significantly faster but only in the shallow condition (Supplementary Fig. S1). We found no significant effect of stimulation on recognition accuracy for targets or nontargets.

Free recall performance

As for recognition, we found a significant main effect of stimulation on free recall ($F_{(4, 490)} = 8.57$, $P < 0.001$, $\eta^2 = 0.07$), with increased recall of targets ($F_{(2, 245)} = 14.42$, $P < 0.001$, $\eta^2 = 0.11$) and reduced recall of nontargets ($F_{(2, 245)} = 4.49$, $P = 0.01$, $\eta^2 = 0.04$). We also found a significant interaction between stimulation and encoding depth ($F_{(8, 490)} = 3.41$, $P < 0.001$, $\eta^2 = 0.05$) with the effect of stimulation on targets ($F_{(4, 245)} = 4.24$, $P = 0.002$, $\eta^2 = 0.07$) or nontargets ($F_{(4, 245)} = 3.39$, $P = 0.01$, $\eta^2 = 0.05$) depending on encoding depth. Posthoc tests revealed that compared to sham or right DLPFC stimulation,

Table 2. Current mood of the sample as assessed with the positive and negative affect schedule (PANAS). Higher scores indicate more positive (or more negative) mood.

		Sham ($n = 126$)		Left DLPFC ($n = 64$)		Right DLPFC ($n = 64$)	
		M	SD	M	SD	M	SD
Shallow	Positive affect	31.00	4.44	28.81	4.97	30.80	4.92
	Negative affect	9.93	1.13	10.10	1.41	9.75	1.02
Deep	Positive affect	29.75	5.15	30.52	4.66	30.79	5.08
	Negative affect	10.55	1.23	10.81	3.62	9.88	1.51
Emotional	Positive affect	30.48	4.31	29.81	3.60	30.45	4.54
	Negative affect	9.52	1.77	10.14	1.49	9.40	0.94

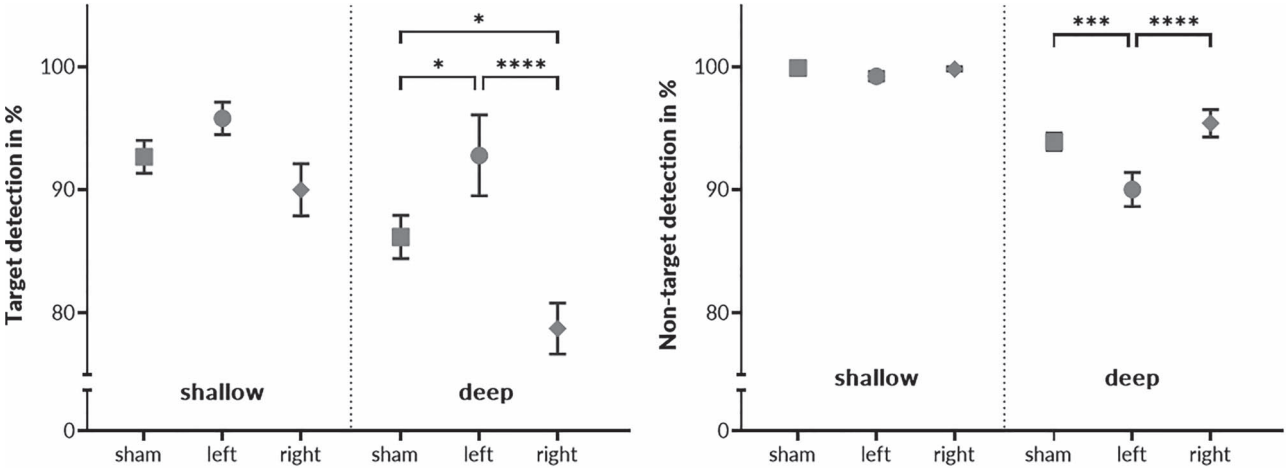

Fig. 3. Decision accuracy during the first encoding run of shallow or deep processing in healthy young volunteers receiving tDCS of the left (gray circles) or right (gray diamonds) DLPFC. Error bars indicate ±1 standard error of the mean. Significant at $P < 0.05$*, $P < 0.001$***, or $P < 0.0001$**** (corrected for multiple comparisons).

stimulation of the left DLPFC significantly increased free recall of targets ($P < 0.001$) and significantly reduced free recall of nontargets ($P < 0.01$), but only in the deep processing condition (Fig. 4).

Free recall performance of emotionally valenced stimuli

Finally, we examined free recall in the context of emotional processing. To this end, we distinguished free recall of words subjectively to have positive or negative valence from neutral words. Again, we found a significant main effect of stimulation ($F_{(6, 158)} = 3.45$, $P = 0.003$, $\eta^2 = 0.12$) as stimulation modulated free recall of positive ($F_{(2, 80)} = 4.79$, $P = 0.01$, $\eta^2 = 0.11$) or negative ($F_{(2, 80)} = 3.23$, $P = 0.04$, $\eta^2 = 0.08$) but not neutral words. Posthoc comparisons revealed that, compared to both sham and right DLPFC stimulation, stimulation of the left DLPFC significantly increased free recall of words that were initially rated as positive ($P < 0.001$, Fig. 5). In contrast, words that were initially rated as negative were better remembered with stimulation of the right DLPFC, in contrast to stimulation of the left DLPFC ($P < 0.05$, Fig. 5).

Alertness task

We found a trend towards a significant main effect of time ($F_{(2,244)} = 2.96$, $P = 0.05$), since response times in intrinsic alertness but not phasic alertness changed with repeated assessments. We did not find a significant interaction of time and stimulation, indicating that stimulation had no significant effect on the change in reaction times. However, we did find a significant main effect of stimulation ($F_{(4,490)} = 8.43$, $P < 0.001$). Posthoc tests revealed that, compared to sham ($P < 0.001$) and left DLPFC stimulation ($P < 0.01$), stimulation of the right DLPFC significantly decreased reaction times during phasic and intrinsic alertness in both the first and the second session (Fig. 6). This indicates that with stimulation of the right DLPFC, participants were more awake or alert.

Discussion

Here we comprehensively examined the influence of left or right DLPFC activity at encoding on episodic memory formation. We show in healthy young adults that memory traces for relevant semantic information became stronger, and their retrieval better, when left—but not right—DLPFC function was enhanced at encoding. This substantially adds to lesion studies, rat, and monkey experiments that had indicated that left and right prefrontal cortex govern encoding of episodic memories and their retrieval from the hippocampus

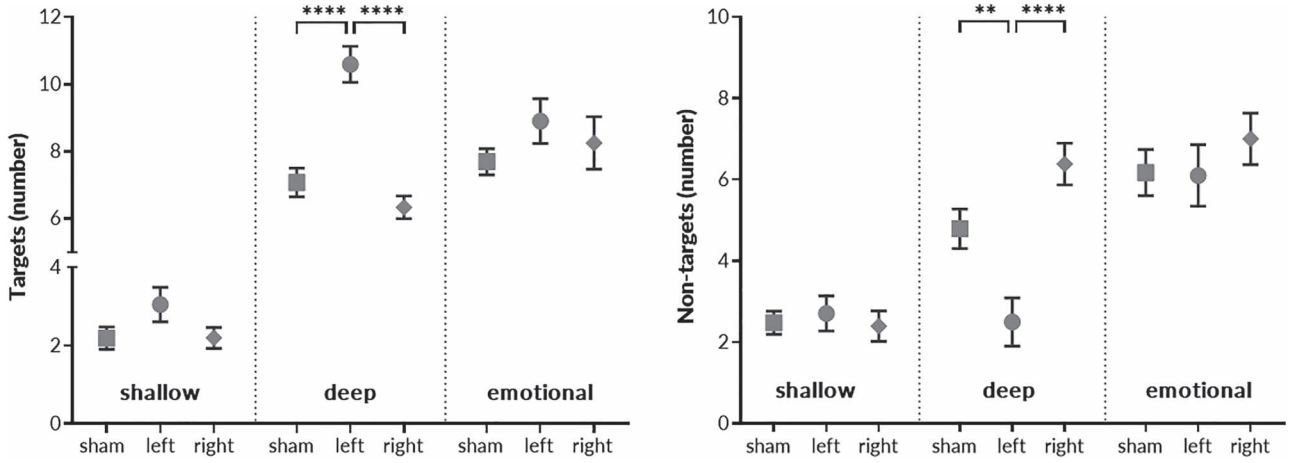

Fig. 4. Number of freely recalled targets or nontargets after shallow, deep, or emotional processing in healthy young volunteers receiving tDCS of the left (gray circles) or right (gray diamonds) DLPFC. Error bars indicate ±1 standard error of the mean. Significant at $P < 0.01$** or $P < 0.0001$*** (corrected for multiple comparisons).

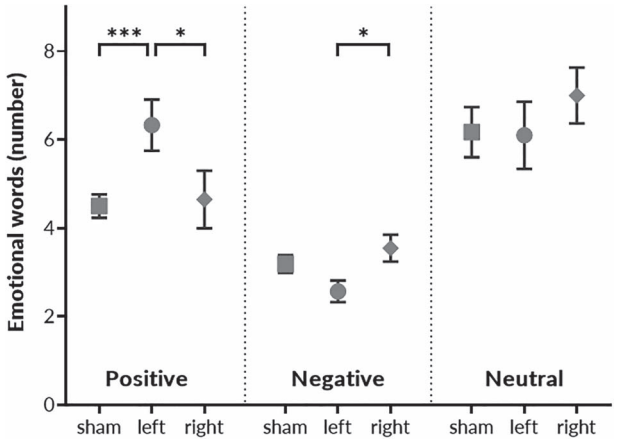

Fig. 5. Freely recalled words that were subjectively perceived to have positive, negative, or neutral content in healthy young volunteers receiving tDCS of the left (gray circles) or right (gray diamonds) DLPFC. Error bars indicate ±1 standard error of the mean. Significant at $P < 0.05$* or $P < 0.001$*** (corrected for multiple comparisons).

(Miller and Cohen 2001; Eichenbaum 2017). In contrast, our data indicate that, at encoding, mainly the left DLPFC acts as a gate keeper for establishing lasting memories of semantic information judged to be relevant. If we assume that the left DLPFC plays an important role for the formation of new memories based on their meaning, this could explain why DLPFC modulation had no influence on shallow processing as shallow processing involved an evaluation of the properties of a word but not its meaning. Our results are in accord with theories that the DLPFC evaluates information to guide response selection towards certain "rules" (in our case decisions whether a word belongs to a category) (Miller and Cohen 2001; Lesh et al. 2011). In a neuro-anatomical network involving the parietal cortex and the anterior cingulate cortex (Lesh et al. 2011), the DLPFC maintains these rules online to promote the selection of relevant responses while suppressing those deemed irrelevant. Within this network, the parietal cortex determines when to shift the attentional focus while the anterior cingulate cortex signals when control-related activity should be increased (Lesh et al. 2011). Our data from dynamically modulating DLPFC function in healthy young adults indicate that the left hemisphere selects relevant information, which subsequently modifies episodic memory formation and retention (Fig. 7). Functionally, the selection may influence the strength of synaptic connections within the neural activity patterns present at encoding, and their partial reactivation at retrieval with the subsequent promotion of episodic memory formation. This view is supported by data from models in which optogenetic and chemogenetic activation or suppression of neural network function influenced recall performance (Josselyn et al. 2015; Richards and Frankland 2017). To modulate network function in our human participants we have used tDCS, a noninvasive brain stimulation method that is able to shape endogenous synaptic plasticity (Kronberg et al. 2017). Our results in humans therefore complement the concepts that had been established from models and suggest that enhancing the activation of neural patterns in the left DLPFC at encoding promotes memory persistence (Richards and Frankland 2017).

Our second important finding is that enhancing left, but not right, DLPFC activity had a selective effect when content was emotionally valenced, promoting persistence of positive while selecting against negative content. This agrees with the role of the left DLPFC in the valence-specific hypothesis but not with that of the right DLPFC, and it does not support the right-hemisphere hypothesis. In a network that involves the cingulate cortex and the parietal cortex, the DLPFC helps monitor processes relevant for the cognitive appraisal of emotional stimuli and guides decisions about memory persistence and transience influenced by current mood states (Fig. 7) (Lewis et al. 2005; Fitzgerald et al. 2011). This helps individuals determine how relevant any new information is in the context of their current mood. Our data are congruent with our participants' emotionally balanced, nondepressed mood

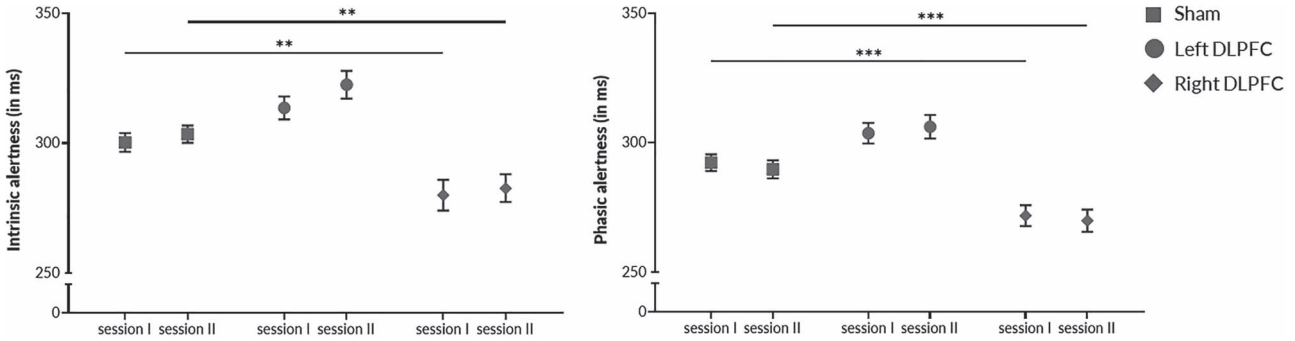

Fig. 6. Reaction times (in milliseconds, ms) during phasic or intrinsic alertness while healthy young volunteers received stimulation of the left (gray circles) or right (gray diamonds) DLPFC. Error bars indicate ±1 standard error of the mean. Significant at $P < 0.01$** or $P < 0.001$*** (corrected for multiple comparisons).

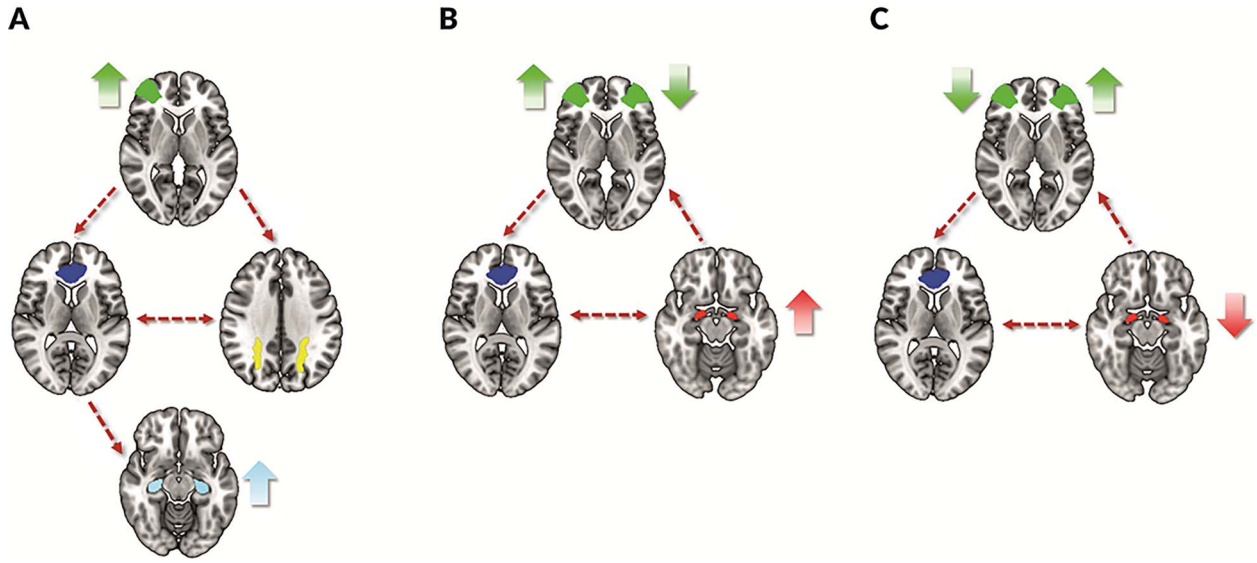

Fig. 7. Model of cognitive control for memory formation of semantic content (A) in a network of the left DLPFC (green) the anterior cingulate cortex (dark blue), the parietal cortex (yellow), and the hippocampus (light blue). Increased activity in the left DLPFC will lead to increased activity in the hippocampus, thereby increasing episodic memory formation. Model of emotional processing in health (B) or disease (C) with increased or decreased activity in the DLPFC and, consequently increased or decreased activity in the amygdala (red) leading to emotional (dys)regulation.

state and confirm previous observations indicating that, physiologically, the left DLPFC supports a bias towards encoding positively, and against encoding negatively valenced information, to maintain healthy brain states (Lewis et al. 2005; Fitzgerald et al. 2011). Increasing activity of the left DLPFC in our study further enhanced this bias towards positively valenced episodic memory formation. In contrast, increasing activity of the right DLPFC seemed to induce a brain state similar to that of depression—in which the right DLPFC is hyperactive while the left DLPFC is hypoactive (Grimm et al. 2008)—shifting the balance of episodic memory formation towards negatively valenced information (Fig. 7). Our data, therefore, suggest that in healthy people an active left DLPFC and a less active right DLPFC at the encoding stage contribute to the mood congruent selection in favor of forming positive and against forming negative memory traces. The differential role of the left DLPFC in the mood congruent formation of memories of emotionally valenced information, as indicated by our data, may contribute to understanding what goes wrong in patients with depression or anxiety who have a tendency to remember more negatively valenced information than healthy individuals (Gollan et al. 2016; Vicario et al. 2019). Our data show that hemispheric lateralization in the DLPFC is physiologically present in healthy people and does not result from a disease process. Hence, the processes causing diseases such as depression or anxiety may affect the healthy lateralization of DLPFC function. This is supported by findings of elevated activity in the right DLPFC and reduced activity in the left DLPFC in both depression and anxiety (Grimm et al. 2008; Vicario et al. 2019). In addition, enhancing left DLPFC function with tDCS reduced processing of negatively valenced information (Brunoni et al. 2014) and successful treatment with antidepressants enhanced activity in the left DLPFC (Kennedy et al. 2001).

Conclusion

Together, these findings provide strong support of a concept that the left DLPFC is key to processing information

at encoding to exert cognitive control over episodic memory formation and retention in humans. If alertness were driving the effects of stimulation on memory encoding, we would have expected the most pronounced effects on episodic memory following right DLPFC stimulation. However, while alertness improved with stimulation, episodic memory formation did not. In contrast, by the same argument stimulation of the left DLPFC did not have a major effect on alertness so the effects on memory encoding and retrieval are most likely mediated by the modulation of the encoding process itself. Active attempts to suppress the retrieval of potentially harmful memories are also important to minimize their impact on mental well-being and avoid their consolidation. Such efforts involve the right DLPFC and its connections to the hippocampus (for a schematic see Fig. 7) (Anderson and Hulbert 2021). Modulation at the encoding phase as in our study will therefore not have influenced the important contribution of the right DLPFC to selective retrieval. Our data from young healthy emotionally balanced adults add to what is known about other hemispheric asymmetries such as in language or perception (Mitchell 2005; Cowell 2010). Our direct observations of the effects of differential left and right DLPFC function modulation during encoding suggest a model of human DLPFC lateralization in which the left DLPFC contributes to assessing relevant semantic properties of new memory content at encoding and thus influences how successful new memories can be retained. The right DLPFC, in contrast, contributes less at the encoding stage but may influence memory retrieval and consolidation. Our model of the differential roles of left and right DLPFC in episodic memory persistence and transience suggests that, in depression or anxiety, at encoding treatments should strive to boost left DLPFC function and decrease right DLPFC activity to reduce the formation of negative memories and help re-establish homeostasis of DLPFC lateralization. In contrast, at the retrieval and consolidation stage right DLPFC function should be enhanced. For any treatment that aims to modulate DLPFC function, it therefore matters that such treatments are applied mindful of the differences in episodic memory formation, retention, and transience.

Limitations

A limitation could be the parallel-group design rather than a cross-over design that would have allowed a direct comparison of stimulation effects. However, a cross-over design in memory tasks can lead to learning effects, which are difficult to distinguish from stimulation effects. For incidental learning tasks, testing an individual twice means the task is no longer incidental but intentional (since the participant already knows what the task will be). Another limitation may be that we randomized at each study site separately rather than across the whole study and that we merged the 2 sham groups. However, we found no statistical difference between the participants at the 2 study sites regarding age, sex, IQ, BDI-II score, hours or quality of sleep before the study, or mood. Likewise, when we tried to predict study site in a binary logistic regression, none of these variables made a significant contribution (classification accuracy: 57%). Thus, we did not find any evidence to suggest that participants systematically differed between sites. In addition, when we analyzed the sham groups separately, results were similar with no significant differences between the sham conditions. Another limitation may be that we did not directly assess what happened between encoding and retrieval. A simulation of the current flow at the level of the hippocampus shows that stimulation did not reach the hippocampus directly. It is therefore more likely that stimulation modulated the DLPFC alone, but we cannot exclude indirect effects perhaps via its connections to the hippocampus.

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Supplementary material

Supplementary material can be found at *Cerebral Cortex* online.

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