The effects of transcranial direct current stimulation on the brain networks related to creative thinking

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Abstract

Creative thinking generating novel and valuable ideas is unique to humans. Recent research has clarified the contribution of different brain networks (Default Mode Network, DN; Executive Control Network; Salience Network) to creative thinking. However, the effects of brain stimulation on the interaction of brain networks during creative thinking and on creative performance have not been clarified. The present study was designed to examine the changes in functional connectivity (FC) and effective connectivity (EC) of the large-scale brain network, and the ensuing changes in creative performance, induced by transcranial direct current stimulation (tDCS). Sixteen healthy male students underwent two tDCS sessions, one with actual stimulation and one with sham stimulation, on two separate days. Participants underwent tDCS (anode over the left dorsolateral prefrontal cortex, DLPFC; cathode over the right inferior parietal lobule, IPL) for 20 minutes. Before and after the tDCS session, electroencephalography signals were acquired from 32 electrodes over the whole head during the creative thinking task. On the FC analysis, the delta band FC between posterior cingulate cortex and IPL significantly increased only after real stimulation. We also found that the change in alpha band FC between IPL and lateral temporal cortex was significantly correlated with the change of flexibility score. On the EC analysis, increased flow of higher frequency oscillations within a large-scale brain network and decreased flow within the DN were observed. Our results reveal that tDCS could change brain network interactions related to creative thinking and modulate the key FC in the generation of flexible creative ideas.

1 Introduction

Creativity is commonly defined as the ability to generate knowledge or work that is novel and useful (Sternberg and Lubart, 1996; Diedrich et al., 2015). Correspondingly, creative thinking consists of two processes: production of novel ideas, and evaluation or selection of those that are useful. Self-produced novel ideas can often occur in the mental state where the person's cognitive attention has shifted from the external to the internal world. Physiologically, the default mode network (DN) is associated with such internal mental state. The DN was originally identified as a set of brain regions activated during the resting state (Shulman et al., 1997), but recently its activation during internally oriented tasks such as episodic memory retrieval and autobiographical future thinking has been reported (Buckner et al., 2008; Spreng et al., 2009; Andrews-Hanna, 2012). The DN is composed of functionally different brain network subsystems: the core DN subsystem (DN_{CORE}); the medial

temporal lobe (MTL)-centered DN subsystem (DN_{MTL}); the third DN subsystem (DN_{SUB3}) (Andrews-Hanna et al., 2010; Christoff et al., 2016). The DN_{CORE} consists of the anterior medial prefrontal cortex (amPFC), posterior cingulate cortex (PCC), and posterior inferior parietal lobule (pIPL); it acts as a hub within the DN and has a key role in internally-directed cognition. The DN_{MTL} mainly consists of the hippocampal formation (HF) and parahippocampal cortex (PHC), and is characterized by its function in memory and simulation of the future (Addis et al., 2007; Andrews-Hanna et al., 2014). The DN_{SUB3} consists of the dorsomedial PFC (dmPFC), lateral temporal cortex (LTC), temporopolar cortex (TPC), and parts of the inferior frontal gyrus (IFG); its role in the DN is currently unclear. The evaluation of self-produced ideas involves dynamic shifts between the two ends of the spectrum of constraints: automatic and deliberate constraints (Christoff et al., 2016). When something salient captures the attention, self-produced thoughts are automatically constrained, or, in other words, the focus of the thoughts automatically shifts from the internal to the external world. The salience network (Salience), mainly consisting of the anterior insula (AI) and the anterior cingulate cortex (ACC), has been proposed to detect both external and internal salient events (Seeley et al., 2007). Shifts of attention and thought also occur under deliberate cognitive control. Such cognitive control has been linked to the executive control network (ECN), mainly consisting of the dorsolateral PFC (DLPFC) and the anterior IPL (aIPL) (Vincent et al., 2008; Niendam et al., 2012). The ECN is involved in both internally and externally oriented thoughts and can couple with the DN flexibly to support goal-directed cognition (Spreng et al., 2010; Dixon et al., 2014). The ECN implements deliberate constraints on thought, and also mediates the interactions between other brain networks (Christoff et al., 2016). Previous neuroimaging studies of creativity were mainly based on electroencephalography (EEG) and functional magnetic resonance imaging (fMRI), and have clarified the contribution of such large-scale brain network to creative thinking. However, most neuroimaging research has focused on correlational methods, while the causal relationships between connectivity patterns and creative performance have not been established.

Besides the research on the neural correlates of creative thinking, several previous studies investigated the possibility of enhancing creativity through brain stimulation (Lucchiari et al., 2018). In particular, transcranial direct current stimulation (tDCS) has been applied to increase or decrease the cerebral activity related to creative thinking. tDCS has an impact not only on the target brain areas, but also on other areas and networks during both tasks and rest (Lang et al., 2005; Keeser et al., 2011; Polanía et al., 2011; Meinzer et al., 2012; Axelrod et al., 2015; Kajimura et al., 2016). However, since creativity is a complex construct that applies to a huge variety of situations, studies on the enhancement of creativity often produce inconsistent results. Furthermore, little is known about how brain areas interact with each other to generate creative ideas because none of these studies combined brain stimulation techniques with neuroimaging. Thus, it is difficult to determine whether the performance changes are caused by the excited/inhibited areas or by a compensatory network mechanism that may be triggered by such perturbations. Caroline et al (Luft et al., 2014) suggested the importance of combining brain stimulation methods with neuroimaging techniques and of employing state-of-the-art connectivity data analysis techniques to obtain a deeper understanding of the underlying spatiotemporal dynamics of connectivity patterns and creative performance.

A previous study (Kajimura et al., 2016) suggested that applying tDCS on the left LPFC/right IPL (r-IPL) may affect the balance of the whole DN system, changing the attention focus and thus promoting or inhibiting imaginative processes. In addition, Axelrod et al (Axelrod et al., 2015) reported that applying anodal tDCS on the left DLPFC (l-DLPFC) promotes task-unrelated thoughts and argued that this stimulation may indirectly affect the DN. Considering these previous studies and the role of ECN in mediating the interactions between brain networks, we hypothesized that

anodal/cathodal stimulation of the l-DLPFC/ r-IPL could modulate the system balance of the large-scale brain network, causally affecting creative thinking.

2 Materials and methods

2.1 Participants

Sixteen male subjects without diseases, brain-related disorders, or eyesight abnormalities participated in the experiment. The two participants with the highest sleepiness scores according to the Stanford Sleepiness Scale, assessed during the experiment, were excluded from the analysis. The remaining 14 participants (23 ± 1.9 years old) were all right-handed. The research was approved by the Research Ethics Committee of the Graduate School of Engineering of the University of Tokyo (approval number: KE18-28) and was conducted in accordance with the Declaration of Helsinki. The participants were informed of the purpose of the study and gave their consent in writing. Since we do not have consent of the participants to publish the data, we cannot share the data. The study was also conducted in accordance with the report of the Committee on Brain Stimulation in Japan (Ugawa et al., 2011) and with internationally accepted safety standards (Nitsche et al., 2003; Poreisz et al., 2007). The experiment was conducted in a laboratory within a few minutes walking distance from the University of Tokyo Hospital, and in case of any discomfort, it was possible to stop the experiment immediately, but no adverse event was observed.

2.2 tDCS

tDCS was applied to the participant's scalp through a saline-soaked pair of sponge electrodes (5×7 cm) connected to a DC-Stimulator 1×1 tES device (Soterix Medical Inc, New York, USA). Electrodes were located according to the extended 10-20 international system for EEG, based on previous reports (Axelrod et al., 2015; Kajimura et al., 2016). The anode was placed over F3, corresponding to the left DLPFC, and the cathode over P4, corresponding to the r-IPL. Real direct current stimulation (Real-Stim) consisted of a constant 2 mA current (current density: 0.057 mA/cm^2) applied for 20 minutes with 30-second fade-in and fade-out. Previous studies have suggested that cortical excitability is stable for at least 1 hour after a 20-min stimulation (Nitsche and Paulus, 2001). Participants perceived the direct current as an itching sensation at the anode contact point at the beginning of the stimulation. To produce sham stimulation (Sham-Stim), the DC-Stimulator has a built-in placebo mode. The electrodes were placed in the same arrangement, but the current stimulation was only delivered for the 30-second ramp up and the 30-second ramp down at the beginning and the end, to mimic the somatosensory artifacts of real stimulation (DaSilva et al., 2011). In the sham condition, the participants received no current for the rest of the 20-min stimulation period, thus experiencing the itching sensation only at the beginning. This procedure makes it possible to keep participants blind to their stimulation condition. In this study, no subject recognized that one stimulus condition was a sham.

2.3 Assessment of individual creativity performances

The paper-and-pencil version of the Alternative Uses Task (AUT) (Guilford et al., 1978) was used. The AUT is widely used in creativity research and is meant to measure the participants' ability for divergent thinking, which represents the best characterization of creative potential (Runco and Acar, 2012). In the AUT, an everyday object was presented, and the participants were instructed to write down as many alternative uses as possible for the object, different from its common use. Before the task, participants were shown the alternative uses of a newspaper, as an example, and practiced writing down the alternative uses of a chair for 1 minute. We selected 20 objects frequently used in

previous studies (Rossmann and Fink, 2010; Glenn Dutcher, 2012; Lee and Therriault, 2013; Zmigrod et al., 2015; Yamaoka and Yukawa, 2016) and performed 4 types of AUT (A, B, C, and D) for the 4 conditions (Pre/Post Real-Stim and Pre/Post Sham-Stim) (Table 1). Each type of AUT consisted of 5 objects with a time limit of 2 min per object, counterbalanced among the participants. Creativity was scored along three dimensions: fluency (the ability to produce a large number of ideas), flexibility (the ability to produce diverse categories of ideas), and originality (the ability to produce novel and unique ideas) (Guilford et al., 1978). Three university students (2 males and 1 female) were hired as judges to rate flexibility and originality.

The creativity score of each condition was calculated as follows:

a. Fluency: the average number of relevant answers for each everyday object.

b. Flexibility: the judges were instructed to evaluate in how many categories the answers for each everyday object could be classified. The average score of five objects evaluated by three judges was calculated as the score of the task.

c. Originality: the judges rated the answers for each object regarding their novelty and uniqueness. Specifically, the judges were instructed to evaluate the originality of the answers on a five-point rating scale ranging from 1 (not original at all) to 5 (highly original) (De Dreu et al., 2008; Silvia et al., 2008). The average score of the answers was calculated as the score of each object. Then, the average score of five objects, evaluated by three judges, was calculated as the score of the task.

Table 1 List of 20 objects used in the four types of the Alternative Uses Task (AUT)

type	A	B	C	D
object	milk bottle	knife	chopsticks	shoe
	rubber balloon	cardboard	phone book	clip
	socks	screwdriver	brick	rope
	wire hanger	ping-pong ball	can	cork
	towel	cloth button	ballpoint pen	CD-ROM

2.4 Experimental procedure

All participants underwent both Real-Stim and Sham-Stim on two separate days, each for 20 minutes, with an interval of three or more days between the experimental sessions. The experiment consisted of a stimulation session and two EEG recording sessions before and after it, with a 5-10 min break between sessions (Fig. 1). The EEG/tDCS device attachment/removal and sleepiness questionnaires were conducted during the break. During the EEG recording session, we measured EEG for 15 min while the participant was answering the AUT, and for 1 min during the resting state, with eyes open, before the AUT. During the tDCS session, the participants watched a driving scene of a car taken by the drive recorder and verbally answered when they noticed a change in driving scene, in order to prevent sleep. The order of the types of tDCS (Real-Stim and Sham-Stim) and the order of the types of AUT (A, B, C and D) was counterbalanced among the participants to take into account the order effect.

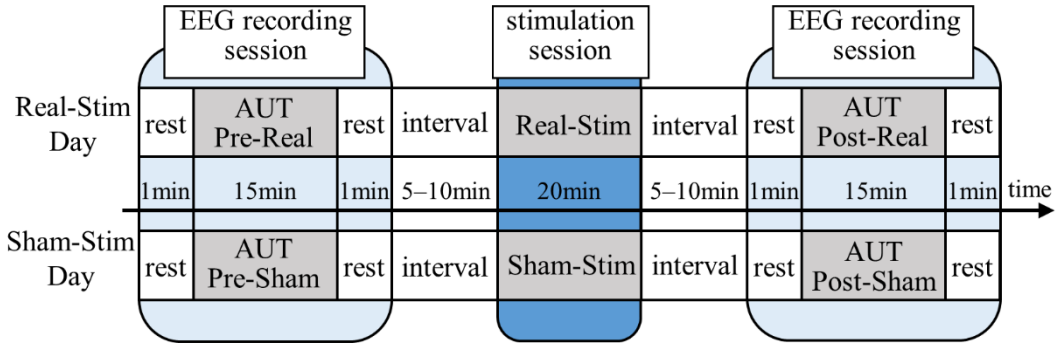

Fig. 1 Experimentalparadigm. Real-Stim, real direct current stimulation; Sham-Stim, sham stimulation.

2.5 EEG measurement and preprocessing

EEG was recorded using the BrainAmp DC (Brain Products) and Brain Vision Recorder (Brain Products) from 32 places over the whole head according to the International 10-20 system (Fp1/2, F7/8, F3/4, Fz, FT9/10, FC 5/6, FC 1/2, T 7/8, C 3/4, Cz, CP 5/6, CP 1/2, TP 9/10, P7/8, P3/4, Pz, O1/2, and Oz) using the ActiCap (Brain Products) with silver-silver chloride active electrodes. During EEG measurements, the electrode located at Fpz was used as ground and the one located at FCz as the system reference. The sampling frequency was 500 Hz, the time constant was 10 s, and the high cut filter was 1000 Hz.

The data were analyzed offline using MATLAB 2016b and EEGLAB (Delorme and Makeig, 2004) version 14.1.b. Recorded EEG signals were bandpass-filtered between 0.5 Hz and 100 Hz using the FIR filter (EEGLAB function “pop_eegfiltnew.m”). Power line fluctuations at 50 Hz were removed using a notch filter (EEGLAB function “pop_cleanline.m”). Electrooculographic (EOG) and electromyographic (EMG) artifacts were removed using the Automatic Subspace Reconstruction (ASR) method (EEGLAB function “clean_rawdata.m” (Mullen et al., 2015; Chang et al., 2018)). The ASR threshold was set at 15 standard deviations based on the recommended value range from the EEGLAB website (Makoto’s preprocessing pipeline), with all other parameters turned off. EEG data epochs during the AUT (5 objects × 2 min) were extracted. The EEG data were re-referenced to a common average reference.

2.6 Connectivity analysis

Exact low resolution brain electromagnetic tomography (eLORETA, LORETA Key software version 20181107 (Pascual-Marqui et al., 1994)) was used to compute the connectivity strength between estimated cortical signals from multichannel head-surface EEG data (Pascual-Marqui et al., 2011). We chose eLORETA because of its accurate estimation of the intracortical distribution of current source density, effectively reducing the effects of volume conduction (Pascual-Marqui et al., 2014b). Validation of LORETA for localization agreement with multimodal imaging techniques has been reported in several studies (Worrell et al., 2000; Mulert et al., 2004; Zumsteg et al., 2005). Further, previous studies have reported that eLORETA can be used to estimate deep brain source activities, including hippocampus and anterior cingulate cortex (Cannon et al., 2004; Pizzagalli et al., 2004). The head model and electrode coordinates were based on the Montreal Neurologic Institute average

MRI brain (MRI152) (Fonov et al., 2011). The solution space was restricted to the cortical gray matter (6239 voxels at 5×5×5 mm spatial resolution). In order to estimate connectivity between core regions of the large-scale brain networks (DN subsystems, Salience, and ECN), 11 cortical regions of interest (ROIs) were selected (Table 2). The connectivity between all pairs of ROIs was computed for five frequency bands: δ (0.5–3.5 Hz); θ (4–7.5 Hz); α (8–12.5 Hz); β (13–30 Hz); and γ (30.5–60 Hz).

Table 2

List of 11 cortical regions of interest (ROIs) selected for connectivity analyses

ROI	MNI coordinate			Anatomical Region	Brain Network
	x	y	z		
1	0	55	10	frontal lobe, medial prefrontal cortex (mPFC)	DN_{CORE}
2	0	-50	25	limbic lobe, posterior cingulate cortex (PCC)	DN_{CORE}
3	-45	-45	35	left parietal lobe, inferior parietal lobule (l-IPL)	DN_{CORE}
4	45	-50	35	right parietal lobe, inferior parietal lobule (r-IPL)	DN_{CORE}
5	-20	-25	-10	left limbic lobe, hippocampus (l-HF)	DN_{MTL}
6	20	-25	-10	right limbic lobe, hippocampus (r-HF)	DN_{MTL}
7	-55	-15	-20	left temporal lobe, lateral temporal cortex (l-LTC)	DN_{SUB3}
8	55	-15	-20	right temporal lobe, lateral temporal cortex (r-LTC)	DN_{SUB3}
9	0	30	20	limbic lobe, anterior cingulate cortex (ACC)	Salience
10	-40	40	25	left frontal lobe, dorsolateral prefrontal cortex (l-DLPFC)	ECN
11	40	40	25	right frontal lobe, dorsolateral prefrontal cortex (r-DLPFC)	ECN

DN, default mode network; DNCORE, core DN subsystem; DNMTL, medial temporal lobe-centered DN subsystem; DNSUB3, third DN subsystem; Salience, salience network; ECN, executive control network

Functional connectivity (FC) was analyzed using Lagged Phase Synchronization (LPS). LPS has been widely used to investigate electrophysiological connectivity (Canuet et al., 2011; Hata et al., 2016; Imperatori et al., 2017). Since detailed information on eLORETA LPS has been previously described (Pascual-Marqui et al., 2011), here we summarize the method. LPS performs a discrete Fourier transform of two signals followed by normalization to evaluate the similarity of the signals in a specific frequency band. The equations representing LPS between signals *x* and *y* are:

$$\boldsymbol{\varphi}_{x,y}^{2}(\boldsymbol{\omega}) = \frac{\{\boldsymbol{Im}[\boldsymbol{f}_{x,y}(\boldsymbol{\omega})]\}^{2}}{\mathbf{1}-\{\boldsymbol{Re}[\boldsymbol{f}_{x,y}(\boldsymbol{\omega})]\}^{2}} \quad (1)$$

$$\boldsymbol{f_{x,y}(\omega)} = \frac{\boldsymbol{S_{xy\omega}}}{\sqrt{\boldsymbol{S_{xx\omega}S_{yy\omega}}}} \qquad (2)$$

where $S_{xx\omega}$, $S_{xy\omega}$, and $S_{yy\omega}$ represent complex valued covariance matrices, and f_{xy} is the complex-valued coherence. LPS is considered to accurately represent FC, as it excludes the instantaneous phase synchronization due to non-physiological artifacts and volume conduction.

Effective directional connectivity (EC) was assessed with the isolated effective coherence (iCoh). This EC analysis is performed at the source level, so it requires EEG source localization (Grech et al., 2008; Jatoi et al., 2014). Since details of the iCoh method have been previously described (Pascual-Marqui et al., 2014b, 2014a), we briefly summarize it. The equation representing iCoh is:

$$\boldsymbol{K_{i\leftarrow j}(\omega)} = \frac{\boldsymbol{S_{\varepsilon ii}^{-1}\left|\breve{A}(\omega)_{ij}\right|^2}}{\boldsymbol{S_{\varepsilon ii}^{-1}\left|\breve{A}(\omega)_{ij}\right|^2 + S_{\varepsilon jj}^{-1}\left|\breve{A}(\omega)_{jj}\right|^2}} \quad (3)$$

where $K_{i\leftarrow j}(\omega)$ is the iCoh value at a given frequency ω between ROI i and j, the arrow indicating that j influences i. $\breve{A}(\omega)$ is the discrete Fourier transform matrix derived by least square fitting of the MVAR model of order p (estimated by the Akaike information criterion). S_ε is the covariance matrix of the residual errors of the MVAR model. The LORETA software is able to automatically compute all the parameters in this equation, producing an iCoh spectrum as output, when provided with EEG data as input (Pascual-Marqui et al., 2014a). In our case, the optional parameter p of the MVAR model was set to 8.

3 Results

3.1 FC changes during creative thinking (Post-Stim vs Pre-Stim)

On Real-Stim, an increased δ band FC between posterior cingulate cortex (PCC) and r-IPL (t = 4.50, corrected $p < 0.05$) was observed (Fig. 2). No significant changes were observed in the other frequency bands. On Sham-Stim, there were no significant differences in FC in any frequency band.

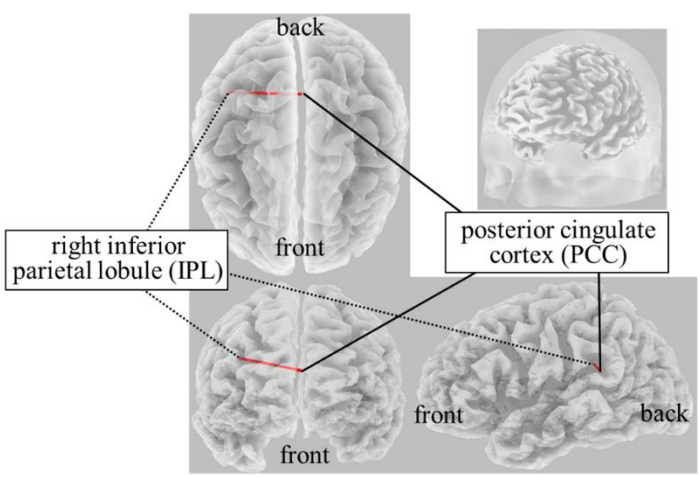

Fig. 2 Result of eLORETA for the comparison of functional connectivity in the delta frequency band between pre- and post-tDCS. The red line indicates the connection showing increased LPS after tDCS (corrected p < 0.05).

3.2 Correlation between FC changes and creative thinking score change

On Real-Stim, the change of the α-band FC between right lateral temporal cortex (r-LTC) and r-IPL (Fig. 3) was strongly and positively correlated with the change in flexibility score (Spearman's *rho* = 0.876, *p* = 4.05e-5). There was no correlation between this connectivity and the other creativity scores (fluency and originality). Fig. 4 shows the correlation between the change of α-band FC (r-IPL and r-LTC) and the change of flexibility score on Real-Stim. No significant correlations were found between changes in creativity scores and FC changes in the other frequency bands. On Sham-Stim, there was no significant correlation between FC changes and changes in creativity score.

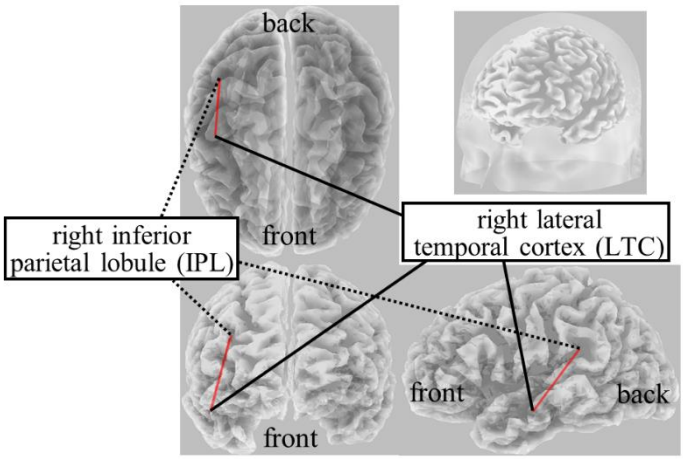

Fig. 3 Functional connectivity between r-LTC and r-IPL in the alpha frequency band. This connectivity was strongly correlated with flexibility score changes

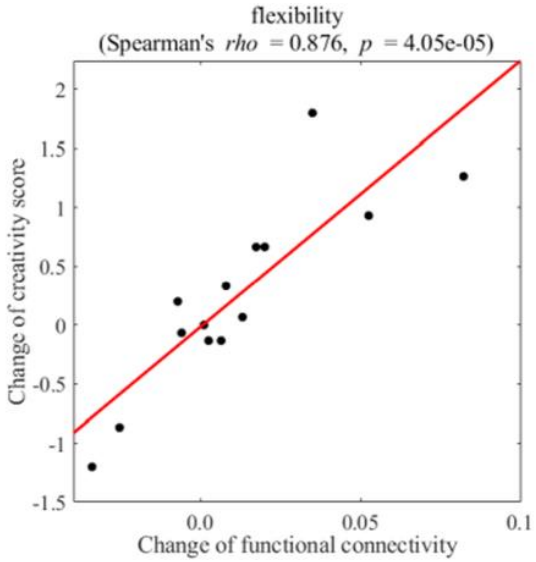

Fig. 4 Correlation between the change of alpha-band functional connectivity between r-IPL and r-LTC and the change in flexibility score upon Real-Stim. The scatterplot shows the data of each participant. The red line indicates the least-squares regression line.

3.3 Change of EC during creative thinking (Post-Stim vs Pre-Stim)

3.3.1 Real-Stim

The significant differences between Post-Real and Pre-Real are shown in Fig. 5. The statistical comparison of connections between Post-Real and Pre-Real showed a complex pattern, with information flow significantly increased or decreased in many connections. Fig. 6 summarizes the main statistically significant results. In general, increased connections were more numerous than decreased ones. At the level of brain networks, three major characteristics were observed during creative thinking at Post-Real compared with Pre-Real: increase of γ flow between multiple brain networks; flow increase from ECN to all DN subsystems; and flow decrease from the left DN subsystems (DN_{MTL} and DN_{SUB3}) to the right ones.

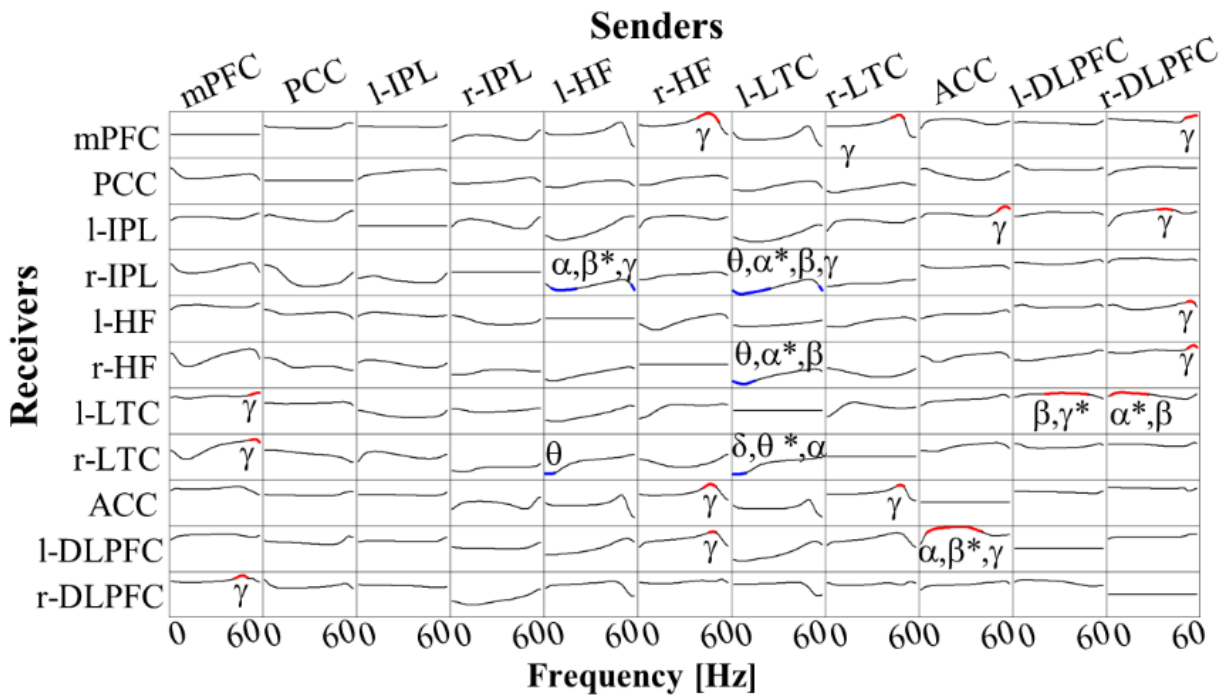

Fig. 5 t-statistic for the comparison of post-Real and pre-Real isolated effective coherence (iCoh) during creative thinking for 14 participants, in 11 regions of interest (ROIs): mPFC, medialprefrontal cortex; PCC, posterior cingulate cortex; l-IPL/r-IPL, left and right inferior parietal lobule; l-HF/r-HF, left and right hippocampus, l-LTC/r-LTC, left and right lateral temporal cortex; ACC, anterior cingulate cortex; l-DLPFC/r-DLPFC, left and right dorsolateral prefrontal cortex. Frequency axis: 0-60 Hz. Frequency bands: δ, 0.5–3.5 Hz; θ, 4–7.5 Hz; α, 8–12.5 Hz; β, 13–30 Hz; γ, 30.5–60 Hz. Corrected p = 0.05 corresponds to a t-threshold of 3.62, with the vertical axis spanning from -4.7 to +4.7. Blue (red) color indicates significantly larger values in Pre-Real (Post-Real). The most significant oscillation is indicated with a superscript "*".

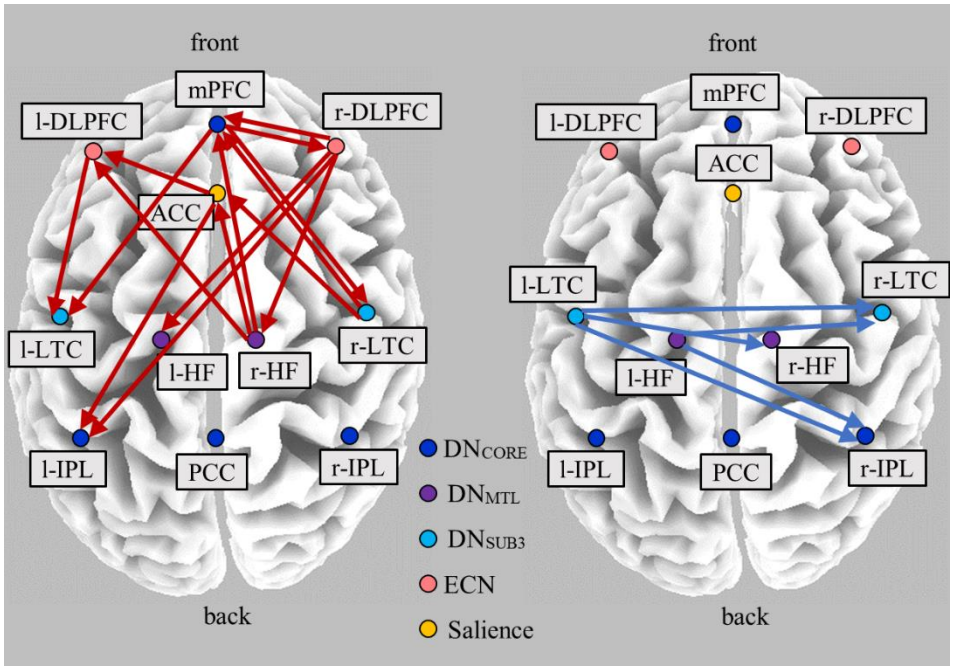

Fig. 6 Statistical comparison of information flow obtained with isolated effective coherence (iCoh). mPFC, medialprefrontal cortex; PCC, posterior cingulate cortex; l-IPL/r-IPL, left and right inferior parietal lobule; l-HF/r-HF, left and right hippocampus, l-LTC/r-LTC, left and right lateral temporal cortex; ACC, anterior cingulate cortex; l-DLPFC/r-DLPFC, left and right dorsolateral prefrontal cortex. ROI, region of interest; DN, default mode network; DNCORE, core DN subsystem; DNMTL, medial temporal lobe-centered DN subsystem; DNSUB3, third DN subsystem; Salience, Salience network; ECN, executive control network. a) red color: significantly larger in Post-Real; b) blue color: significantly larger in Pre-Real.

3.3.2 Sham-Stim

Some significantly increased connections were also observed upon Sham-Stim, as shown in Fig. 7. The main statistically significant results are summarized in Fig. 8. No connectivity was decreased. At the level of brain networks, two major characteristics were observed during creative thinking at Post-Sham compared with Pre-Sham: higher frequency (β and γ) flow increase from ECN to DN_{MTL} and DN_{SUB3}; and higher frequency (α, β and γ) flow increase from DN_{SUB3} to DN_{CORE}, Salience, and ECN.

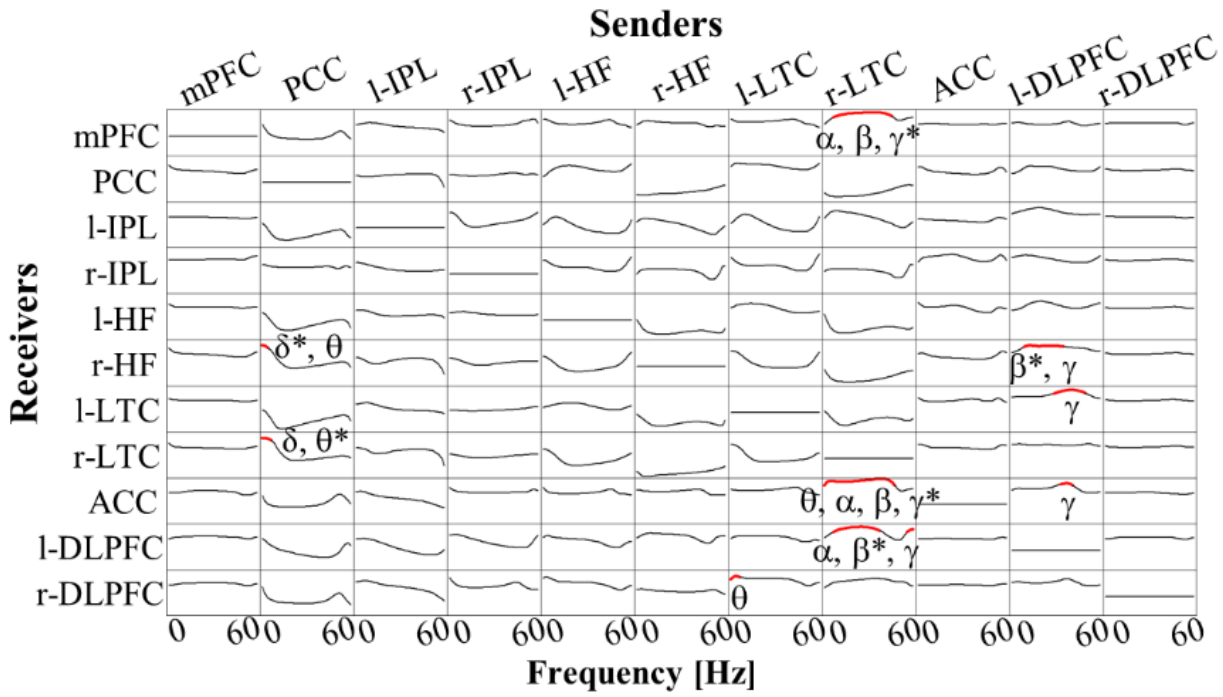

Fig. 7 t-statistic for the comparison of post-Sham and pre-Sham isolated effective coherence (iCoh) during creative thinking for 14 participants, in 11 regions of interest (ROIs). mPFC, medialprefrontal cortex; PCC, posterior cingulate cortex; l-IPL/r-IPL, left and right inferior parietal lobule; l-HF/r-HF, left and right hippocampus, l-LTC/r-LTC, left and right lateral temporal cortex; ACC, anterior cingulate cortex; l-DLPFC/r-DLPFC, left and right dorsolateral prefrontal cortex. Frequency axis: 0-60 Hz. Frequency bands: δ, 0.5–3.5 Hz; θ, 4–7.5 Hz; α, 8–12.5 Hz; β, 13–30 Hz; γ, 30.5–60 Hz. Corrected p = 0.05 corresponds to a t-threshold of 3.57, with vertical axis spanning from -3.2 to +4.6. Blue (red) color indicates significantly larger values in Pre-Sham (Post-Sham). The most significant oscillation is indicated with a superscript "*".

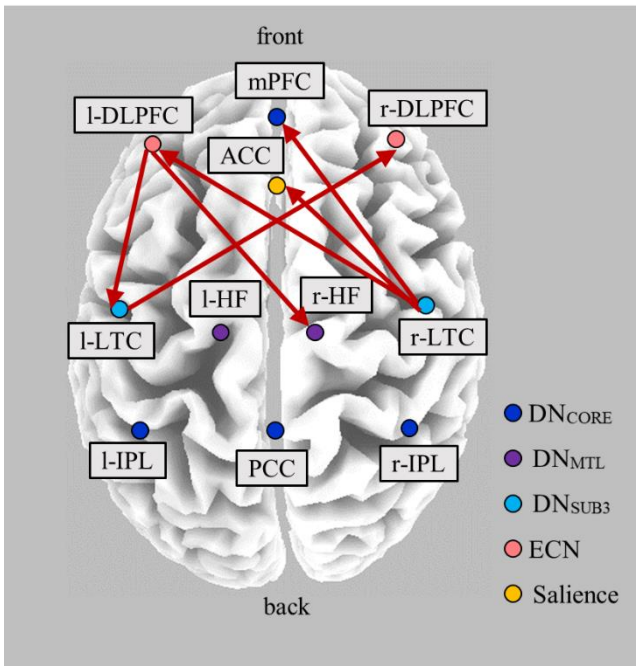

Fig. 8 Statistical comparison of information flow obtained with isolated effective coherence (iCoh). mPFC, medialprefrontal cortex; PCC, posterior cingulate cortex; l-IPL/r-IPL, left and right inferior parietal lobule; l-HF/r-HF, left and right hippocampus, l-LTC/r-LTC, left and right lateral temporal cortex; ACC, anterior cingulate cortex; l-DLPFC/r-DLPFC, left and right dorsolateral prefrontal cortex. ROI, region of interest; DN, default mode network; DNCORE, core DN subsystem; DNMTL, medial temporal lobe-centered DN subsystem; DNSUB3, third DN subsystem; Salience, Salience network; ECN, executive control network. Red color: significantly larger in Post-Sham.

4 Discussion

Here, we investigated the causal relationships between the application of tDCS (anode over l-DLPFC and cathode over r-IPL), changes in connectivity of the large-scale brain network related to creative thinking, and changes in creative performance. We found that applying tDCS increased δ-band FC between r-IPL (DN_{CORE}) and PCC (DN_{CORE}), and affected the EC of the large-scale brain network related to creative thinking. Furthermore, the change of α-band FC between r-IPL (DN_{CORE}) and r-LTC (DN_{SUB3}) induced by tDCS is reflected in a change in creative thinking flexibility. The present study is the first to investigate the effects of tDCS on the large-scale brain network (EEG-index) related to creative thinking, and their causal relationships with creative performance.

The r-IPL and PCC both belong to the DN_{CORE}, which acts as a hub within the DN and contributes to internally-directed cognition (Christoff et al., 2016). r-IPL and PCC are both activated when we remember past events or imagine future ones (Addis et al., 2007; Abraham et al., 2008). A previous fMRI study also reported that the FC between right PCC and r-IPL significantly increased during AUT compared with a control task consisting in generating typical properties of everyday objects (Beaty et al., 2015). Therefore, it is possible that during AUT participants remember past experiences or imagine future events in which the everyday object is used for alternative purposes. The present

finding may indicate that the increase in FC between r-IPL and PCC induced by tDCS causally facilitates the first creative thinking process, namely the production of ideas, during AUT.

Furthermore, the change in α-band FC between r-IPL and r-LTC had strong positive correlation with the change in creative thinking flexibility. The r-LTC is a core brain region of DN_{DUB3} and the exact anatomical region selected as ROI in this study is the right middle temporal gyrus (r-MTG). Several previous results support a right hemisphere bias of the MTG for insight (Subramaniam et al., 2009; Cranford and Moss, 2011; Sakaki and Niki, 2011; Wu et al., 2013). When people encounter words, they think about the related information (Jung-Beeman, 2005). "Semantic activation" provides access to semantic representations, activation features, and first order associations of the input words. This semantic activation depends on Wernicke's areas in both hemispheres, and especially the posterior middle and superior temporal gyrus. The left hemisphere strongly activates small and focused semantic fields containing information closely related to the dominant meaning of the input words. In contrast, the right hemisphere weakly activates large diffuse semantic fields, containing distant and unusual semantic features that seems unrelated to the input words, providing coarse interpretation (Jung-Beeman, 2005). During AUT in this study, participants encountered a word representing an everyday object and were asked to think about as many alternative uses as possible. It is possible that the participants were searching for semantically distant related words. Considering the role of r-LTC in distant semantic activation and the role of r-IPL in internal oriented cognition, the strength of the functional connection between these two DN regions may causally affect the flexibility of creative thinking.

In the EC analysis, almost all the flow increases upon Real-Stim were in the γ frequency band, and increased γ-band flows were also observed upon Sham-Stim. However, on Real-Stim, the increased γ–band flow originated from the whole brain network (Salience, ECN, and 3 DN subsystems), and both HFs were receivers of γ-band flow from r-DLPFC. Recent neuroimaging studies have demonstrated that the interaction between DLPFC and HF is implicated in working memory (Liu et al., 2014; Chen et al., 2017b). The DLPFC plays a critical role by exerting executive top-down control over the other working memory-related brain areas. In a previous study (Chen et al., 2017a), the FC strength between DLPFC and HF was significantly associated with working memory performance, while other studies have suggested that working memory is related to or benefits creative thinking (Vandervert et al., 2007; De Dreu et al., 2012). The working memory capacity benefits creativity because it enables the individual to maintain focus on the task and prevents undesirable mind wandering (De Dreu et al., 2012). Therefore, we can conclude that tDCS facilitated the executive control function of the DLPFC on working memory, thus modifying the brain state during creative thinking. Not only the deliberate constraints, but also the sources of variability and the automatic constraints from ACC (Salience) were changed by Real-Stim.

The flow from l-LTC (DN_{SUB3}) and l-HF (DN_{MTL}) to the right DN subsystem decreased only after Real-Stim. Considering that the change in FC between r-IPL (DN_{CORE}) and r-LTC (DN_{SUB3}) showed strong positive correlation with the change in flexibility score, these decreased flows within the DN may have causally affected the outputting of flexible ideas. The MTL has long been linked to episodic memory (Ranganath et al., 2004; Squire et al., 2004; Addis et al., 2007; Buckner et al., 2008). The MTL, and especially HFs, have also been linked to semantic memory recently and it has been suggested that the HF, involved in spatial search in animals, may work in semantic space (network) search in humans (Zhang et al., 2008; Duff et al., 2020). It is known that human memory is stored in a conceptual semantic network structure, organized along the lines of semantic similarity (Collins and Loftus, 1975). Considering the role of the r-LTC in distant semantic activation and the

role of the HF in semantic memory, the Real-Stim may have affected the semantic processing role of DN during AUT.

There were some significant flow increases upon Sham-Stim, which we attribute to the placebo effect. In the sham condition, the current stimulation was delivered only at the beginning and the end, to mimic the somatosensory artifacts of Real-Stim (DaSilva et al., 2011). An interview was conducted after the experiment, and no subject recognized that one stimulus condition was a sham. Some participants responded that they felt that AUT became easier to answer after Sham-Stim. Regardless of the stim condition (Real-Stim or Sham-Stim), the expectation of the effects of tDCS may have affected brain conditions. The total flow from the ECN was significantly increased in the higher frequency band in both conditions. Higher frequency (β and γ) EEG oscillation is often linked to top-down control, decision making, or cognitive functions. This result could support the notion that the flow from the ECN is related to deliberate constraints. Furthermore, the higher-frequency flow increase from r-LTC (DN_{SUB3}) to mPFC (DN_{CORE}) and ACC (DN_{CORE}) were observed on both Real-Stim and Sham-Stim. These flows may also be related to deliberate constraints.

This study has some limitations. First, the sample was small and biased, for instance, in terms of sex and age range, which may have affected the robustness of the results. Second, there is no control stimulation in terms of polarity or region. Therefore, it is difficult to definitively link our findings to the specific target regions stimulated. Third, the size of the electrodes used for tDCS was relatively large, making it difficult to perform exact and focal stimulation of the l-DLPFC and r-IPL. Thus, the current results should be replicated using more targeted neurostimulation techniques, such as High-Definition tDCS (Edwards et al., 2013). Fourth, we selected and analyzed only certain brain regions, but other regions may be involved in creative thinking. However, we identified some mechanism underlying creative thinking after tDCS.

5 Conclusions

The current study used connectivity analyses to investigate how tDCS affects the large-scale brain network related to creative thinking. Our findings provide some new evidence into the neural mechanism of creative thinking, and especially flexibility. Future research is needed to clarify the causal relationship between mechanism and creative performance, also with the aim of devising methods for the enhancement of creativity.

6 Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

7 Author contributions

KK, KU and ZL contributed conception and design of the study. MN supervised the study. KK and ZL conducted the experiment and analyzed the data. KK wrote the first draft of the manuscript. All authors contributed to manuscript revision, read and approved the submitted version.

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We presented the preliminary results of the present study in the following conferences: The 9th International IEEE EMBS Conference on Neural Engineering and LIFE 2019 (Internal conference). Although we analyzed the same experimental data for these conferences, after receiving feedback from other researchers, we changed the analysis method and added new contents in this article.

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