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Martin, Andrew K. and Meinzer, Marcus and Lindenberg, Robert and Sieg, Mira M. and Nachtigall, Laura and Flöel, Agnes (2017) Effects of transcranial direct current stimulation on neural networks in young and older adults. Journal of Cognitive Neuroscience, 29 (11). pp. 1817-1828. ISSN 0898-929X.

DOI

https://doi.org/10.1162/jocn_a_01166

Link to record in KAR

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Document Version

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Effects of Transcranial Direct Current Stimulation on Neural Networks in Young and Older Adults

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Abstract

■ Transcranial direct current stimulation (tDCS) may be a viable tool to improve motor and cognitive function in advanced age. However, although a number of studies have demonstrated improved cognitive performance in older adults, other studies have failed to show restorative effects. The neural effects of beneficial stimulation response in both age groups is lacking. In the current study, tDCS was administered during simultaneous fMRI in 42 healthy young and older participants. Semantic word generation and motor speech baseline tasks were used to investigate behavioral and neural effects of uni- and bihemispheric motor cortex tDCS in a three-way, crossover, sham tDCS controlled design. Independent components analysis assessed differences in task-related activity between the two age groups and tDCS effects at the network level. We also explored whether laterality of language network organization was effected by tDCS. Behaviorally, both active tDCS conditions significantly improved semantic word retrieval performance in young and older adults and were comparable between groups and stimulation conditions. Network-level tDCS effects were identified in the ventral and dorsal anterior cingulate networks in the combined sample during semantic fluency and motor speech tasks. In addition, a shift toward enhanced left laterality was identified in the older adults for both active stimulation conditions. Thus, tDCS results in common network-level modulations and behavioral improvements for both age groups, with an additional effect of increasing left laterality in older adults. ■

INTRODUCTION

Transcranial direct current stimulation (tDCS) has widely been used to modulate human brain function (Riggall et al., 2015; Dubljevic, Saigle, & Racine, 2014). This noninvasive brain stimulation technique uses a weak electrical current that is administered via two or more scalp attached electrodes. Acute stimulation effects are mediated by transient modulation of the neural resting membrane potential (Stagg & Nitsche, 2011). Moreover, long-lasting beneficial effects on brain function and performance can be achieved by multisession tDCS when combined with motor or cognitive training in healthy individuals (Meinzer, Jahnigen, et al., 2014; Cohen Kadosh, Soskic, Iuculano, Kanai, & Walsh, 2010; Dockery, Hueckel-Weng, Birbaumer, & Plewnia, 2009; Reis et al., 2009) or behavioral treatment in patient populations (Allman et al., 2016; Meinzer, Darkow, Lindenberg, & Flöel, 2016).

Given that tDCS is a relatively low-cost technique and also has an excellent safety profile (Fregni et al., 2015), such studies have raised hope that it may be suited to counteract age-associated functional impairment (for a review, see Perceval, Floel, & Meinzer, 2016; Summers, Kang, & Cauraugh, 2016; Hsu, Ku, Zanto, & Gazzaley, 2015). Importantly, a number of studies have demonstrated that tDCS can restore impaired performance in older individuals to the level of young controls (Panouilleres, Joundi, Brittain, & Jenkinson, 2015; Hardwick & Celnik, 2014; Zimerman, Heise, Gerloff, Cohen, & Hummel, 2014; Meinzer, Lindenberg, Antonenko, Flaisch, & Flöel, 2013). However, other studies failed to demonstrate such "restorative" effects (Fertonani, Brambilla, Cotelli, &Miniussi, 2014; Manenti, Brambilla, Petesi, Ferrari, & Cotelli, 2013) and montages that improved performance in young individuals did not yield the same effects or even impaired performance in older adults (Learmonth, Thut, Benwell, & Harvey, 2015; Nilsson, Lebedev, & Lovden, 2015; Boggio et al., 2010). The latter is not surprising because aging results in substantial structural and functional brain reorganization (Gutchess, 2014; Grady, 2012; Bishop, Lu, & Yankner, 2010) and positive stimulation effects in young individuals may not necessarily induce the same effects in older individuals (Perceval et al., 2016). Thus, information about neural reorganization based on functional imaging may be useful to guide future stimulation protocols in aging or to investigate differential effects of tDCS in young and older adults (Perceval et al., 2016). This can be achieved by administering tDCS during simultaneous fMRI, which allows the parallel assessment of tDCS effects on performance and brain function (Meinzer, Lindenberg, Darkow,

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Journal of Cognitive Neuroscience 29:11, pp. 1817–1828
doi:10.1162/jocn_a_01166

et al., 2014). This technique has successfully been used to assess local and functional network-level effects of tDCS (Darkow, Martin, Wurtz, Flöel, & Meinzer, 2017; Lindenberg, Sieg, Meinzer, Nachtigall, & Flöel, 2016; Meinzer et al., 2013; Meinzer, Antonenko, et al., 2012; Antal, Polania, Schmidt-Samoa, Dechent, & Paulus, 2011; Holland et al., 2011). However, to date, no previous study has directly compared the neural mechanisms by which tDCS modulates brain function in young and older individuals.

In this study, we used intrascanner tDCS to investigate for the first time behavioral and neural network-level tDCS effects during a semantic word retrieval task in both healthy young and older individuals. In young individuals, semantic word retrieval is associated with left lateralized activity primarily in frontal-temporal regions (Gutierrez-Sigut, Payne, & MacSweeney, 2015; de Zubicaray & McMahon, 2009; Heim, Eickhoff, & Amunts, 2009; Jeon, Lee, Kim, & Cho, 2009; Meinzer et al., 2009; Whitney et al., 2009; Spalek & Thompson-Schill, 2008). Older individuals frequently exhibit enhanced activity in prefrontal regions in the nondominant right hemisphere during this task, which was negatively correlated with performance in previous studies (Meinzer et al., 2009, 2013; Meinzer, Seeds, et al., 2012). However, variability in lateralization has also been identified in younger individuals, with greater left laterality typically associated with better performance (Mellet et al., 2014; Meinzer, Flaisch, et al., 2012; Boles, Barth, & Merrill, 2008). Thus, we used independent components analysis, which allows decomposing the fMRI data in maximally independent task-related networks, to explore differences in network-level activation in relation to age group (older vs. young) and stimulation condition (active vs. sham tDCS).

METHODS

Study Overview

All participants completed an overt semantic word generation task during functional MRI with tDCS administered simultaneously to the primary motor cortex (M1). This montage has been shown to improve language function in healthy aging (Meinzer, Lindenberg, Sieg, et al., 2014) and in patients with post-stroke language impairment (Meinzer et al., 2016). The study employed a three-way, sham-controlled, crossover, within-subject design to assess the impact of unilateral and bilateral ("dual tDCS") M1-tDCS on functional network characteristics in both age groups. During each session, participants first completed a resting-state scan followed by the semantic word retrieval task (Please note, results of the resting-state data analysis have been reported previously; Lindenberg et al., 2016; Lindenberg, Nachtigall, Meinzer, Sieg, & Flöel, 2013). The three scanning sessions were separated by approximately 1 week to prevent carryover effects of the active stimulation conditions, and the order of the stimulation conditions was counterbalanced across participants. Data from the older group have been reported (Meinzer, Lindenberg, Sieg, et al., 2014). However, in that study, only univariate fMRI data analyses that could not capture functional network effects were reported. The study was approved by the ethics committee of the Charité University Hospital (Berlin, Germany).

Participants

Twenty-four healthy young adults (12 men, 12 women; mean age = 26.7 ± 3.8) and 18 healthy older adults (9 men, 9 women; mean age = 68.4 ± 5.2 years) were recruited for this study. All participants were right-handed according to the Edinburgh Handedness Inventory (all ≥ 0.9; Oldfield, 1971), had not participated in prior tDCS studies, and did not report psychoactive medication or recreational drug use or a history of current or previous neurological or psychiatric disorder. The majority of young and older participants had a high school degree (13 years of education; young: 19/24, older: 15/18). The remaining had completed at least 11 years of formal education. Before study inclusion, the participants provided written informed consent.

Transcranial Direct Current Stimulation

A constant direct current (1 mA) was administered by an MRI-compatible stimulator (DC-Stimulator Plus, NeuroConn, Ilmenau, Germany) using an established setup (Meinzer, Lindenberg, Darkow, et al., 2014). The anode was always placed inside a 5 × 7 cm^2 saline-soaked sponge pocket and attached over the M1 in all stimulation conditions (C3 of the 10–20 EEG system) as described previously (Lindenberg et al., 2013, 2016; Meinzer, Lindenberg, Sieg, et al., 2014). During the unihemispheric condition, a larger functionally inert reference electrode (10 × 10 cm^2) was positioned over the right supraorbital region. For dual tDCS, the reference electrode (5 × 7 cm^2) was placed over the right M1 (position C4). During sham tDCS, the reference electrode was pseudorandomly assigned to either the right supraorbital region or right M1 in half of the participants.

In all stimulation conditions, the current was initially increased to 1 mA in a ramp-like fashion over 10 sec shortly before the start of the resting-state sequence and remained constant for 30 min during unihemispheric and dual tDCS, thereby covering the entire duration of the language task that took approximately 11 min (see below). During sham tDCS, the current was turned off after 30 sec before the start of the resting-state sequence. In all conditions, the current was ramped down over 10 sec at the end of the stimulation.

fMRI Parameters and Task Characteristics

Magnetic resonance imaging data were acquired using a 3-T Trio MR scanner (Siemens, Erlangen, Germany) at the Berlin Center for Advanced Neuroimaging (Charité University Hospital, Berlin, Germany). Details of the task-related paradigm have been described previously (Meinzer, Lindenberg, Sieg, et al., 2014; Lindenberg et al., 2013). In short, we employed a T2*-weighted EPI sequence (repetition time/acquisition time = 6000/2000 msec): echo time = 30 msec, flip angle = 90°, 32 transverse slices, gap = 0.75 mm, interleaved acquisition, field of view = 192 × 192, acquisition matrix = 64 × 64, 104 volumes) and a temporal sparse sampling design. This allows assessing overt verbal responses during a scanner off phase to avoid articulation related artifacts.

Six semantic categories (six blocks of 10 consecutive trials of the same category, trial duration 3.8 sec) were presented using a projector and system of mirrors. Participants were instructed to produce one exemplar during each trial or respond with "next" if they couldn't think of a response. Between trials, a black screen was displayed (2.2 sec) and the hemodynamic response was acquired (sparse sampling). Task blocks alternated with a simple motor speech baseline condition (saying the word "rest"; five consecutive trials in response to a written cue). Eighteen preselected categories were divided into three sets matched according to published norms and a behavioral pilot study (Set 1: trees, insects, sports, equipment, body parts, beverages, occupations; Set 2: flowers, fish, kitchen appliances, clothing, food, hobbies; Set 3: spices, birds, toys, colors, autoparts, musical instruments (for details, see Meinzer, Lindenberg, Sieg, et al., 2014). Those three sets were counterbalanced across the groups. Before scanning, participants were trained using a different set of categories. During scanning, overt responses were recorded using an MRI-compatible microphone and transcribed for subsequent analysis. Two raters, blinded to the stimulation condition, scored the responses. Incorrect responses (exemplars that do not belong to a given category), omissions, and repetitions of an exemplar (same exemplar, synonyms) were scored as errors. In case of disagreement, a consensus was reached by the two raters. All correct trials were entered into the independent components analysis (ICA) analysis.

Behavioral Analysis

Repeated-measures ANOVA (RM-ANOVA) compared performance levels across the three stimulation conditions with Age group included as a between-subject factor. All comparisons were Bonferroni-corrected.

fMRI Analysis

Preprocessing was performed using Statistical Parametric Modeling (SPM8, Wellcome Department of Imaging Neuroscience, London, UK). Preprocessing of the data was identical as in our previous study (Meinzer, Lindenberg, Sieg, et al., 2014) and comprised realignment of functional images to the first image of the time series, coregistration with the individual participants' anatomical image, unified segmentation and registration to MNI standardized space, and spatial smoothing using an 8 × 8 × 8 mm^3 Gaussian kernel. Design matrices, detailing the onsets of both semantic word retrieval and baseline motor speech tasks, were created for each participant.

To assess differences in task-related functional network structure in both age groups and potential tDCS effects, we used ICA. ICA identifies maximally independent brain networks that constitute the overall BOLD signal. This technique has commonly been used with resting-state data and has identified networks of brain regions that consistently show temporally synchronised BOLD signal fluctuations. These networks are reliable within and between participants with common examples such as the default mode or dorsal attention network. ICA is largely data driven and does not require a priori assumptions about the underlying network structure (Margulies et al., 2010) This approach has also been utilized to understand BOLD fluctuations with regards to cognitive tasks that elicit coordinated activity in specialized subnetworks concerned with different aspects of the task (e.g., motor, visual, or auditory processing; Gess, Fausett, Kearney-Ramos, Kilts, & James, 2014). Incorporating this method into the study of aging and the impact of tDCS may allow the assessment of network-level differences between young and older participants and the assessment of potential differential tDCS effects in both groups.

In this study, ICA was performed using the GIFT toolbox (version 4.0a, icatb.sourceforge.net). For both young and older adults (total n = 42), the preprocessed images were entered into an ICA analysis. Details of the ICA algorithm are outlined in Calhoun, Adali, Pearlson, and Pekar (2001). Briefly, by using a modified minimum description length algorithm (Li et al., 2007) and two PCA steps, the individual fMRI datasets were reduced into 23 spatially independent components. A group spatial ICA was then performed using the infomax algorithm (Bell & Sejnowski, 1995), resulting in independent spatial maps and time courses for every component, subject, and session. The infomax algorithm was then repeated 10 times using ICASSO (Himberg & Hyvarinen, 2003) to improve the reliability of the decomposition. The spatial ICs were then back reconstructed onto each individual. Components were deemed artifacts and removed from consideration if the spectral frequency was disproportionately in the high range compared with other networks or if considerable overlap with white matter and/or cerebrospinal fluid was noted. This also removed components determined to be due to motion or related to physiological noise. This resulted in the removal of six components, leaving 17 components of interest taken into the task-related analysis and a Bonferroni-corrected significance level of $p < .003$ (0.05/17). To determine components associated with either the semantic word retrieval or baseline motor speech tasks, a regression analysis was performed on the ICA time courses, using the design matrix created in SPM within the GIFT software. Movement parameters were included in the regression analysis to control for movement-related artifacts on network-level activation.

Networks Associated with Tasks

To determine networks that were positively modulated by either task, a one-sample *t* test was conducted. Networks identified to have significant positive activation associated with one task and negative activation with the other were considered. This resulted in three networks associated with the semantic word retrieval task and four with the motor speech baseline task (see Tables 1 and 2; Figures 1 and 2).

Network-level Differences between Age groups

Differences in the interaction between task type (semantic word retrieval, motor speech) and age group (young, older) on the mean activity extracted from all nine networks of interest during sham tDCS were analyzed using a 2 × 2 RM-ANOVA in SPSS (v23).

Effects of tDCS on Network-level Activation

Interactions between Age group (young and older), Task (semantic word retrieval and motor speech), and Stimulation condition (sham tDCS, anodal tDCS, and dual tDCS) were analyzed using a 2 × 2 × 3 RM-ANOVA. Stimulation effects independent of age group were also analyzed by combining the samples and performing a 2 × 3 RM-ANOVA on the contrast between Task (semantic word retrieval and motor speech) and Stimulation (sham tDCS, anodal tDCS, dual tDCS).

Laterality Analysis

Direct comparisons of laterality have focused on voxel count measures following univariate analysis of neuroimaging data (Seghier, 2008). In the current study, by utilizing an ICA approach, laterality can be investigated at the network level without needing to consider individual voxel counts or thresholds. A laterality index was computed for all participants by computing the difference between the beta weights of the predominantly left-lateralized frontoparietal network and the predominantly right-lateralized frontoparietal network during the semantic word retrieval task (Geranmayeh, Leech, & Wise, 2016; see Figure 2). Networks were chosen that were comparable to those

Table 1. Peak Activity in Components Identified as Having a Positive Association with Semantic Word Retrieval and a Negative Association with the Motor Speech Baseline Task—Naming Convention: Needs to Be Explained (Overlap with Known Networks/Peak Activity/Extent)

Brain Regions	*Hemisphere*	*Maximum t Values (MNI Coordinates)*	*F Score*	*p*
10 Left frontoparietal			492.9	<.001
Middle frontal gyrus	L	4.7 (−48, 33, 18)		
Inferior frontal gyrus	L	4.6 (−48, 36, 15)		
Superior parietal lobe	L	4.4 (−27, −72, 48)		
Precuneus	L	3.9 (−24, −72, 51)		
Inferior parietal lobule	L	3.1 (−36, −63, 48)		
15 pCC			83.0	<.001
Posterior cingulate gyrus	R	3.5 (3, −69, 12)		
Posterior cingulate gyrus	L	3.4 (−3, −72, 9)		
Cuneus	R	3.4 (3, −72, 9)		
Cuneus	L	3.2 (−3, −69, 6)		
Precuneus	R	2.7 (3, −69, 18)		
22 Dorsal ACC			38.9	<.001
Anterior cingulate gyrus	R	3.4 (3, 36, 12)		
Anterior cingulate gyrus	L	3.1 (−3, 36, 12)		
Medial frontal gyrus	R	2.7 (3, 42, 18)		
Superior frontal gyrus	R	2.6 (27, 57, 6)		
Middle frontal gyrus	R	2.5 (30, 57, 9)		

Table 2. Peak Activity in Components Identified as Having a Positive Association with Motor Speech Baseline Task and a Negative Association with the Semantic Word Retrieval Task

Brain Regions	*Hemisphere*	*Maximum t Values (MNI Coordinates)*	*F Score*	*p*
6 Anterior temporal/insula			99.3	<.001
Superior temporal gyrus	L	4.3 (−39, 9, −18)		
Inferior frontal gyrus	L	3.7 (−36, 9, −15)		
Insula	L	3.4 (−42, −3, −6)		
Superior temporal gyrus	R	3.3 (45, 0, −9)		
Parahippocampal gyrus	L	3.0 (−30, 6, −18)		
12 Ventral ACC			250.0	<.001
Anterior cingulate	L	6.9 (−3, 12, −3)		
Anterior cingulate	R	6.8 (3, 12, −3)		
Caudate	L	5.8 (−6, 12, −6)		
Caudate	R	5.7 (6, 12, 0)		
Medial frontal gyrus	L	3.8 (−3, 27, −12)		
13 Motor			22.71	<.001
Postcentral gyrus	R	3.3 (33, −39, 66)		
Precentral gyrus	R	3.2 (24, −27, 72)		
Postcentral gyrus	L	3.0 (−9, −45, 69)		
Paracentral lobule	L	2.9 (−3, −42, 66)		
Precentral gyrus	L	2.9 (−21, −27, 72)		
17 Default mode			135.58	<.001
Posterior cingulate	L	4.9 (0, −48, 24)		
Cingulate gyrus	L	4.9 (0, −51, 27)		
Precuneus	L	4.7 (0, −63, 36)		
Posterior cingulate	R	4.5 (3, −51, 24)		
Cingulate gyrus	R	4.5 (3, −48, 27)		
11 Right frontoparietal[a]				
Inferior parietal lobule	R	8.3 (42, −53, 52)		
Precuneus	R	4.5 (9, −67, 50)		
Inferior parietal lobe	L	4.2 (−45, −50, 49)		
Superior frontal gyrus	R	3.5 (30, 58, 0)		
Middle frontal gyrus	R	2.7 (45, 17, 43)		

[a]Negatively associated with both semantic fluency and motor speech; however, activation is significantly more during the motor speech task (−0.38 vs. −0.26, $F = 16.31$, $p < .001$).

identified in a previous study by Gess et al. (2014) and containing overlapping regions from univariate studies identifying left laterality in semantic fluency (Gutierrez-Sigut et al., 2015; Heinzel et al., 2013; Meinzer et al., 2009; Gourovitch et al., 2000) and a negative association with up-regulated right frontal regions and semantic fluency performance (Yeung et al., 2016; Meinzer et al., 2009, 2013).

RESULTS

Impact of tDCS on Performance

RM-ANOVA revealed significant differences between the stimulation conditions ($F = 10.77$, $p < .001$, $\eta^2 = 0.36$); however, neither Age group ($F = 0.20$, $p = .66$) nor Age group × Stimulation interactions ($F = 1.33$, $p = .27$) were

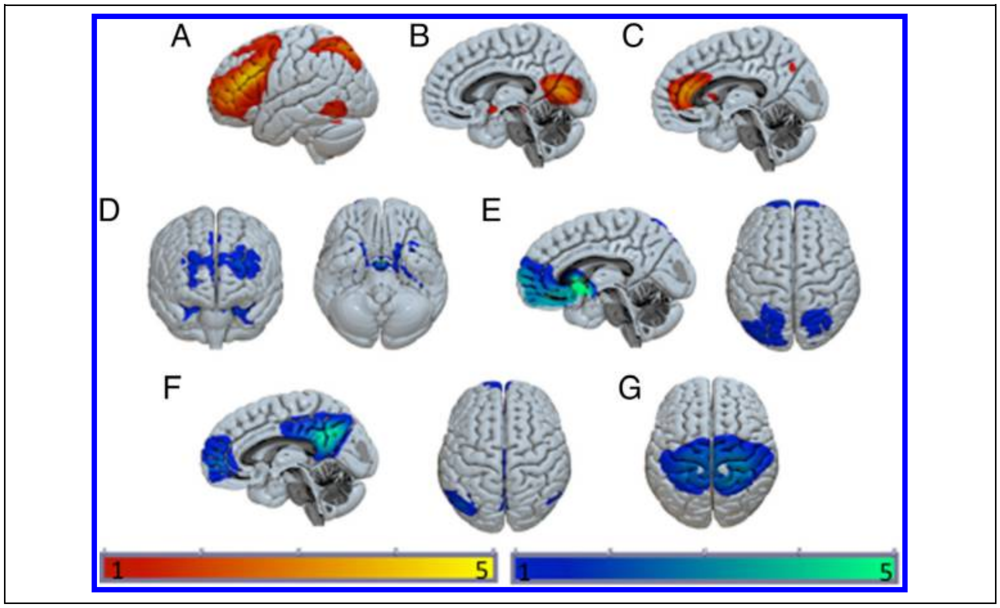


Figure 1. Networks associated with semantic word retrieval (red) or motor speech tasks (blue). Networks associated with greater activation during the semantic fluency task: (A) left frontoparietal network, (B) posterior cingulate network, and (C) dorsal anterior cingulate network. Networks associated with greater activation during motor speech task: (D) insula/anterior temporal network, (E) ventral anterior cingulate/medial frontal network, (F) DMN, and (G) motor network.

significant. Numerically, older participants made more errors during sham tDCS compared with younger individuals (8.0 vs. 6.6), but this difference was not significant (p = .31). Across both age groups, post hoc paired t tests showed that both active stimulation conditions significantly reduced the number of errors on the semantic word retrieval task (anodal vs. sham, 5.2 vs. 7.2, $p < .001$, $\eta^2 = 0.28$; dual vs. sham, 5.0 vs. 7.2, $p < .001$, $\eta^2 = 0.26$). Performance was comparable between the two active stimulation conditions (p = .78; see Figure 3).

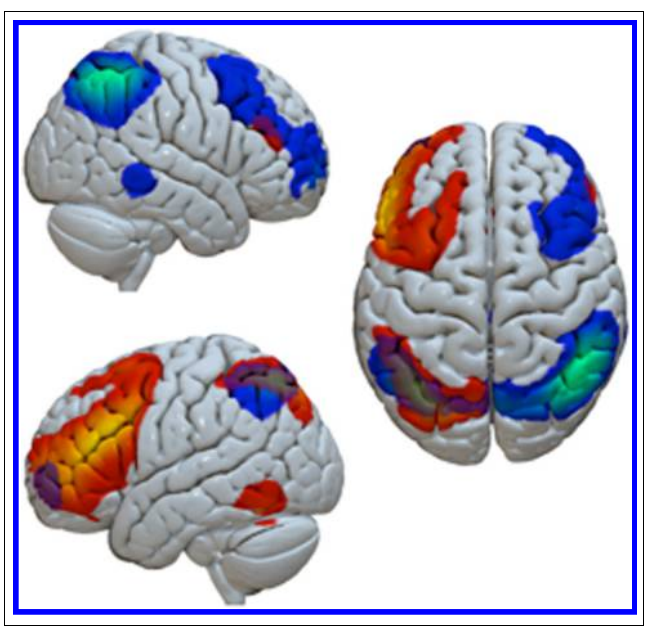


Figure 2. Left- and right-lateralized frontoparietal networks. A laterality index was calculated by computing the difference in beta weights during the semantic word retrieval task.

Network-level Differences in Activation between Age Groups

Activation differences between young and older groups were analyzed for the seven networks associated with semantic word retrieval or the motor speech baseline during sham tDCS (see Tables 1 and 2). The Bonferroni multiple comparison threshold of significance was set at 0.05/7 = 0.007 to correct across the seven networks of interest. The contrast of activation beta weights between task (word retrieval, motor speech) and age group (young, older) identified a significant interaction in the motor ($F = 28.13$, $p < .001$, $\eta^2 = 0.41$; see Figure 4) and default

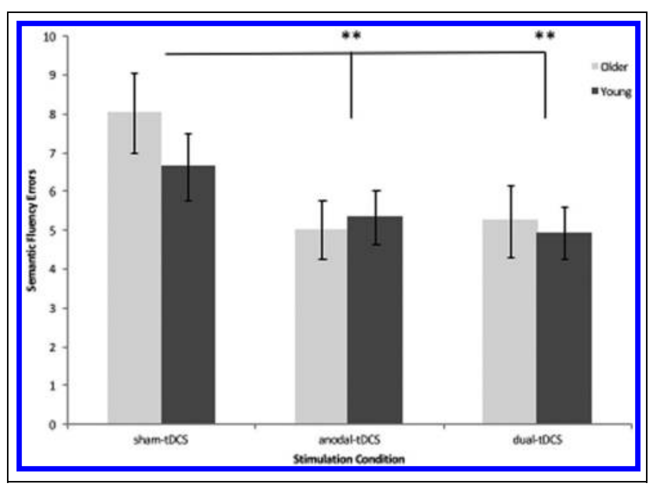


Figure 3. Impact of sham, anodal, and dual tDCS on semantic word retrieval performance (number of errors) for young and old adults. A significant stimulation effect was identified with both anodal and dual tDCS reducing errors compared with sham tDCS. Although the older participants numerically made more errors during sham tDCS (8.0 vs. 6.6), no age effects were significant. Vertical lines represent the standard error of the mean. **$p < .01$.

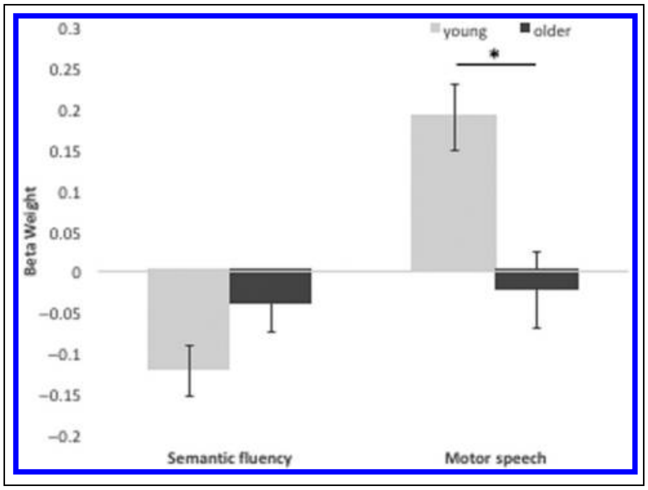


Figure 4. Activation differences in the motor network between young and older adults across the semantic fluency and motor speech tasks during sham tDCS. A significant interaction between group and task was identified. Specifically, young participants had greater activation during the motor speech task and greater deactivation during the semantic fluency task compared with older adults. Vertical lines represent the standard error of the mean. $^{**}p < .01$.

mode networks (DMNs; $F = 18.88$, $p < .001$, $\eta^2 = 0.32$; see Figure 5). Post hoc t tests revealed greater activation of the motor network (0.19 vs. −0.02, $t = 3.39$, $p = .002$, Cohen's $d = 1.04$) during the motor speech task in the younger group. For the DMN, the young adults deactivated the DMN to a greater extent than the older group during the semantic fluency task (−0.33 vs. −0.18, $t = -4.02$, $p < .001$, Cohen's $d = 1.25$).

Stimulation Effects on Network-level Activation

The effects of anodal and dual tDCS were analyzed across all networks of interest. A significant interaction between Stimulation and Task was identified in the ventral ACC, $F = 4.45$, $p = .02$, $\eta^2 = 0.19$, with follow-up analysis revealing that dual tDCS reduced activity of the network during the baseline motor speech task, $t(41) = 3.91$, $p < .001$, Cohen's $d = 0.61$, with a nonsignificant reduction during anodal tDCS, $t(41) = 0.53$, $p = .60$, Cohen's $d = 0.08$ (see Figure 6). The modulation of the ventral ACC network was not correlated with an increase in performance, $r = -.26$, $p = .10$. A significant interaction between stimulation and task was also identified in the dorsal ACC network, $F = 5.18$, $p = .01$, $\eta^2 = 0.21$, with a pattern of reduced activity of the network during the semantic fluency task and increased modulation during the motor speech task for both anodal and dual tDCS (see Figure 7). Follow-up analyses revealed no significant difference for anodal or dual compared with sham, during semantic fluency, $t(41) = -0.47$, $p = .64$, Cohen's $d = -0.08$ and $t(41) = -1.38$, $p = .18$, Cohen's $d = -0.22$, respectively; or during baseline motor speech task, $t(41) = -0.17$, $p = .87$, Cohen's $d = 0.03$, and $t(41) = 1.24$, $p = .22$, Cohen's $d = -0.19$, respectively. No effect of Stimulation condition was identified for the other networks (left frontoparietal, $F = 0.32$, $p = .73$; posterior cingulate cortex [pCC], $F = 0.63$, $p = .54$; anterior temporal/insula, $F = 0.58$, $p = .57$; motor, $F = 3.23$, $p = .05$; DMN, $F = 0.88$, $p = .42$).

Next we assessed whether stimulation had a different effect in the young and older adults. Although network activation differences were identified during sham tDCS between the young and older groups for the motor network and DMN (see above), stimulation had no effect on these or the other five networks of interest. Specifically, there were no significant interactions between Stimulation condition (sham, anodal, dual), Age group (young, older), and Task (word retrieval, motor speech) for activation in any of the networks of interest (left frontoparietal, $F = 0.13$, $p = .29$; pCC, $F = 2.22$, $p = .12$; dorsal ACC, $F = 0.09$, $p = .91$; anterior temporal/insula, $F = 0.05$, $p = .95$; ventral ACC, $F = 1.22$, $p = .31$; motor, $F = 0.93$, $p = .40$; DMN, $F = 1.92$, $p = .16$).

Laterality and Semantic Word Retrieval Performance

The laterality index (i.e., the activation difference between Component 10 [left frontoparietal] and Component 11 [right frontoparietal network]) was significantly correlated with word retrieval performance during sham tDCS; that is, greater laterality was associated with better performance ($r = -.318$, $p = .04$) across all participants. Laterality was greater in the younger group compared with the older group (0.61 vs. 0.19), $t = 7.84$, $p < .001$, Cohen's $d = 2.40$ (see Figure 8). Although the correlation between laterality and performance was stronger in the younger versus older group (−0.385 vs. −0.245),

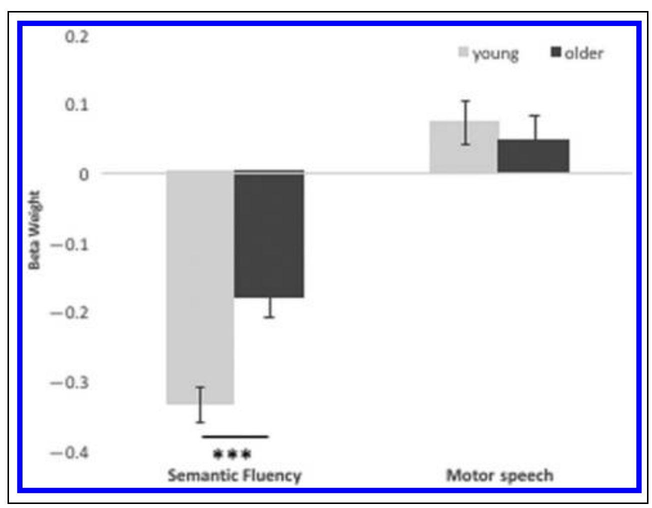


Figure 5. Activation differences in the DMN between young and older adults across the semantic fluency and motor speech tasks. A significant interaction between group and task was identified. Specifically, younger adults deactivated the DMN to a greater extent during the semantic fluency task. Vertical lines represent the standard error of the mean. $^{***}p < .001$.

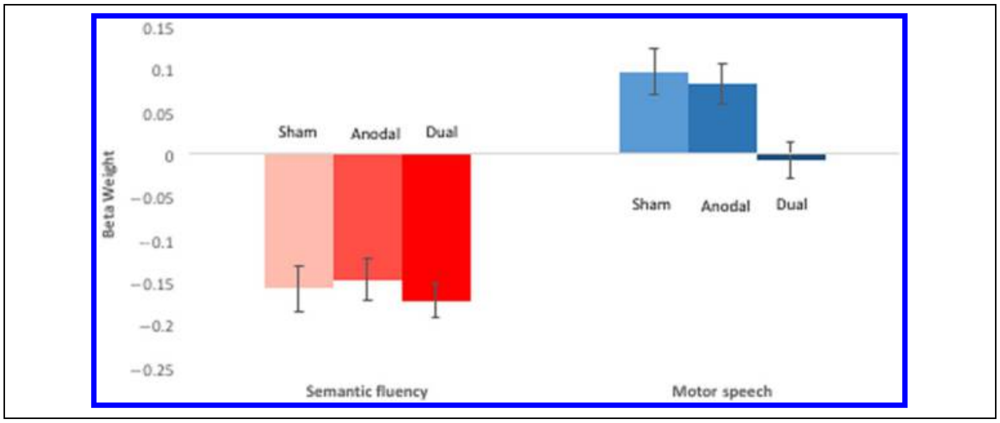


Figure 6. Effect of anodal and dual tDCS on task modulation of the ventral ACC network. An interaction was identified between task and stimulation. Specifically, during the motor speech task, dual tDCS reduced activity compared with both sham and anodal, $p < .001$ and $p = .001$, respectively. Vertical lines represent the standard error of the mean.

no significant differences in correlation strength was observed between the two age groups, $z = 0.46$, $p = .65$.

Stimulation Effects on Left Laterality

Next we assessed whether active tDCS affected left laterality and whether this was dependent on age group. Laterality (sham, anodal, dual) and Task (semantic fluency and motor speech) were included as within-subject measures and Age group as a between-group factor. A significant interaction was identified between Stimulation and Age group, $F(2, 39) = 5.09$, $p = .01$, $\eta^2 = 0.21$ (see Figure 9). Follow-up analysis revealed an increase in left laterality in the older group $F(2, 16) = 4.98$, $p = .02$, $\eta^2 = 0.38$. No change in laterality was found in the younger group, $F(2, 22) = 0.42$, $p = .66$. Laterality shift did not differ between semantic fluency and motor speech tasks, $F(2, 39) = 0.43$, $p = .66$. Order of sessions had no impact on left laterality as indicated by an RM-ANOVA with Stimulation (sham, anodal, and dual) as a within-subject factor and Sham order (first, second, third) entered as a between-subject factor, $F(4, 78) = 0.51$, $p = .73$. There was also no difference depending on age group for this factor, $F(4, 72) = 1.32$, $p = .27$. Therefore, active stimulation increased left lateralization in both the semantic fluency and motor speech tasks in older adults only. No linear correlations were found between changes in laterality and performance in both age groups or the combined sample.

DISCUSSION

In this study, we compared behavioral and neural effects of uni- and bilateral M1-tDCS in healthy young and older adults and investigated for the first time potential neural network effects of stimulation in both age groups. Stimulation resulted in both common and distinct effects in both age groups. Behaviorally, performance improved during both active tDCS conditions in both age groups and modulated activity in both the ventral and dorsal anterior cingulate networks regardless of age group. Moreover, during sham, stronger right lateralization of language-related networks that was observed in the older group during sham tDCS was reduced during active stimulation; that is, tDCS resulted in a leftward shift of processing. This demonstrates that differences in baseline neural organization may result in differential effects on neural network function in young and older individuals.

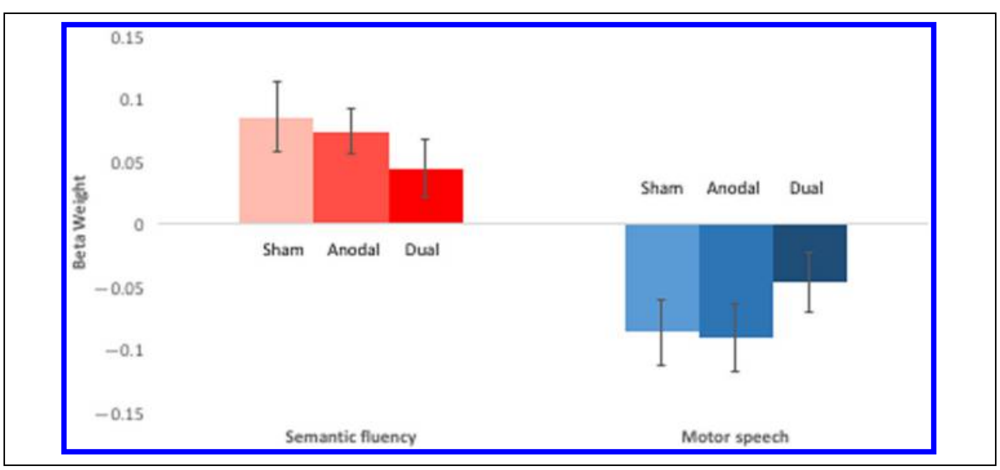
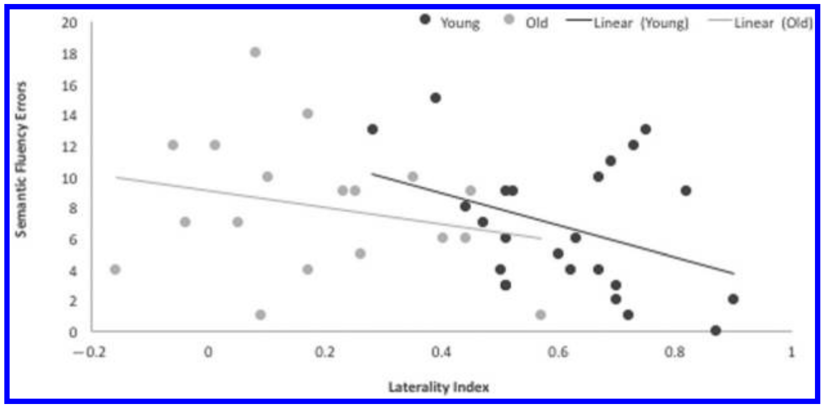


Figure 7. Effect of anodal and dual tDCS on task modulation of the dorsal ACC network. An interaction was identified between task and stimulation. Specifically, dual tDCS reduced activity during the semantic fluency task and increased activity during the motor speech task. Vertical lines represent the standard error of the mean.

Figure 8. Correlation ($r = -.318$, $p = .04$) between laterality index and semantic fluency errors during sham tDCS. The correlation was higher for young adults ($r = -0.385$) compared to old adults ($r = -.245$), although this was not statistically significant, $z = 0.46$, $p = .65$.



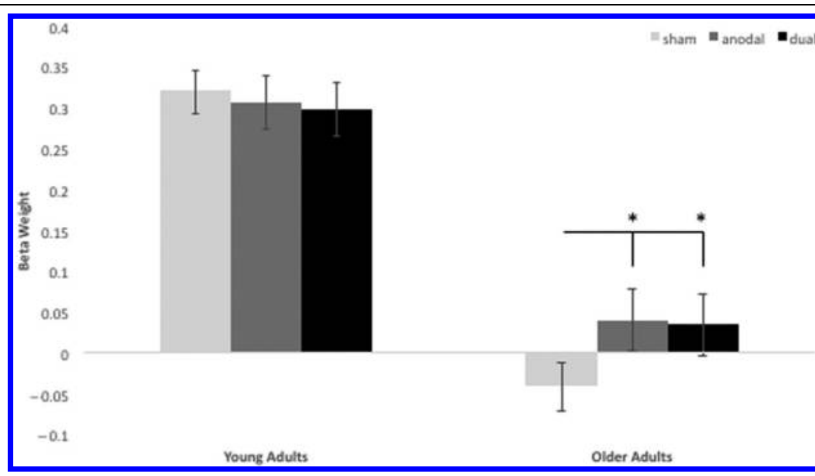
Baseline Neural Network Organization and Impact on tDCS Effects

Previous studies have highlighted that behavioral and neural tDCS effects may not be expressed in a uniform way across groups of participants. For example, motor cortex tDCS yielded highly variable stimulation effects in neurophysiological and neuroimaging studies in both young and older adults (Dyke, Kim, Jackson, & Jackson, 2016; Lindenberg et al., 2013, 2016; Wiethoff, Hamada, & Rothwell, 2014). Similarly, cognitive tDCS effects in both age groups may depend on a number of trait or state-dependent variables (Looi et al., 2016; Learmonth et al., 2015; Sarkar, Dowker, & Cohen Kadosh, 2014; Meinzer et al., 2013; Berryhill & Jones, 2012). However, to date, no previous study has directly investigated age group differences on tDCS response at the functional network level.

This was accomplished for the first time in this study by considering network-level activity modulation and also activation balance between task-relevant functional networks in the left and right hemisphere. Importantly, numerous functional imaging studies have demonstrated reduced lateralization during cognitive tasks in older adults but also highlighted interindividual variability of this process across the lifespan (Mellet et al., 2014; Grady, 2012; Meinzer, Flaisch, et al., 2012; Boles et al., 2008; Cabeza, 2002). This was confirmed in this study by showing that lateralization of language-related functional networks was variable in both age groups. Moreover, across the entire sample, stronger left lateralization was associated with better behavioral performance during the semantic word retrieval task. This result is in line with previous imaging studies employing univariate (local) measures of functional activity that linked enhanced activity in right frontal regions to reduced word retrieval performance (Meinzer, Flaisch, et al., 2012; Meinzer et al., 2009; Persson et al., 2004). Our results also support the theory that efficient cognition relies heavily not only on integration and segregation of functional networks within the brain (Rubinov & Sporns, 2010) but also on an intricate balance between competing networks (Fornito, Zalesky, & Breakspear, 2015; Brem, Fried, Horvath, Robertson, & Pascual-Leone, 2014).

Furthermore, tDCS-induced functional reorganization of task-relevant left lateralization was observed only in older adults. This result lends support to the notion that tDCS may be most effective in individuals with overall lower baseline performance and suboptimal neural

Figure 9. The effects of anodal and dual tDCS on the laterality index for young and older adults. A significant interaction was identified between task and stimulation, such that laterality increased in the older group and decreased in the young group. Follow-up analyses identified a significant increase in the older adults after both anodal and dual tDCS with no effect in the younger adults. Vertical lines represent the standard error of the mean. *$p < .05$.



processing (Looi et al., 2016; Learmonth et al., 2015; Meinzer et al., 2013); that is, in this study expressed as an imbalance between competing brain networks and reduced behavioral performance during sham tDCS in the older group. However, behavioral improvements were also observed in the younger adults, showing that tDCS may also be effective in improving performance in those with high functioning and balanced segregation between brain networks. Reduction in activity in both the ventral and dorsal ACC networks is consistent with evidence from stimulation of the left inferior frontal gyrus in older adults (Meinzer et al., 2013) and reduced activity during active stimulation may reflect decreased attentional or monitoring demands (Meinzer, Seeds, et al., 2012; Carter et al., 2000).

It is important to note that behavioral and neural effects in this study were not achieved by direct stimulation of primary language regions in left temporal cortex as in previous studies (Meinzer, Antonenko, et al., 2012; Cattaneo, Pisoni, & Papagno, 2011; Holland et al., 2011; Sparing, Dafotakis, Meister, Thirugnanasambandam, & Fink, 2008). Rather, we administered anodal tDCS in both active conditions to the left primary motor cortex. Behaviorally, preactivation of the motor network by behavioral interventions or anodal tDCS resulted in improved language processing in healthy individuals and patients with poststroke language impairment (e.g., Meinzer et al., 2016; Benjamin et al., 2014; Meinzer, Lindenberg, Sieg, et al., 2014; Hadar, Wenkert-Olenik, Krauss, & Soroker, 1998). Moreover, inhibitory cathodal M1-tDCS has been shown to interfere with language processing (Liuzzi et al., 2008). However, although this confirms the relevance of motor–language interactions, the neural mechanisms underlying these beneficial behavioral effects are currently unknown.

Given that the left M1 is anatomically and functionally connected to frontotemporal brain regions (Pulvermuller & Fadiga, 2010; Willems & Hagoort, 2007) and mutual interactions between these regions during language production tasks have been demonstrated (Eickhoff, Heim, Zilles, & Amunts, 2009), driving inputs from M1 into interconnected language network nodes are conceivable. However, modeling studies have also demonstrated that different M1 montages result in current spread to prefrontal regions (Kuo et al., 2013). Moreover, functional imaging studies have demonstrated that M1-tDCS modulates activity and connectivity in premotor and prefrontal cortices (Lindenberg et al., 2013, 2016; Antal et al., 2011). This could be an alternative explanation for the positive behavioral or neural effects in this study. This needs to be investigated in future imaging studies using measures of effective connectivity, which allow to investigate the direction of mutual interactions between brain regions (Fornito et al., 2015). Alternatively, high-definition tDCS of the motor cortex has been shown to result in more focal current administration than the conventional montages used in this study (Bortoletto, Rodella, Salvador, Miranda, & Miniussi, 2016; Kuo, Paulus, & Nitsche, 2014) and could be used to test the specificity of the behavioral and neural effects.

Conclusions

In summary, the current study confirmed that M1-tDCS can improve word retrieval across the lifespan and increase left hemispheric laterality in frontoparietal networks in older adults. Understanding the neurophysiological impact of tDCS and differences across the lifespan will ultimately increase its efficacy as a tool for cognitive remediation in healthy adults as well as in patients with age-related pathologies affecting cognition.

Acknowledgments

This work was supported by grants from the Australian Research Council (Marcus Meinzer: ARC FT120100608), the Deutsche Forschungsgemeinschaft (Agnes Flöel: 379-8/1; 379-10/1, 379-11/1, DFG-Exc-257), the Bundesministerium für Bildung und Forschung (Agnes Flöel: FKZ0315673A and 01GY1144; Agnes Flöel and Marcus Meinzer: 01EO0801), and the Else-Kröner Fresenius Stiftung (Robert Lindenberg: 2011-119).

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